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Surprisingly long survival of premature conclusions about naked mole-rat biology

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ABSTRACT

Naked mole-rats express many unusual traits for such a small rodent. Their morphology, social behaviour, physiology, and ageing have been well studied over the past half-century. Many early findings and speculations about this subterranean species persist in the literature, although some have been repeatedly questioned or refuted. While the popularity of this species as a natural-history curiosity, and oversimplified story-telling in science journalism, might have fuelled the perpetuation of such misconceptions, an accurate understanding of their biology is especially important for this new biomedical model organism. We review 28 of these persistent myths about naked mole-rat sensory abilities, ecophysiology, social behaviour, development and ageing, and where possible we explain how these misunderstandings came about.

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I. INTRODUCTION

It is not uncommon for beautiful hypotheses to persist among non-specialists long after contradictory evidence has accumulated. Examples can be found across the sciences from Newton's laws of motion (Newton, 1687) and Bohr's electron shells (Bohr, 1913) to the one gene–one protein hypothesis (Beadle & Tatum, 1941), and early ideas regarding haplodiploid eusociality (Hamilton, 1964). The popular representation of science is that it is as continuously self-correcting as *Wikipedia*, but once a hypothesis has gained popularity, it can take considerable time and evidence to displace it (Kuhn, 1970). We here attempt to combat such informational inertia by systematically reviewing the state of understanding for one area of science in which there is much perpetuation of beautiful, but falsified, hypotheses: the naked mole-rat *Heterocephalus glaber*. Some of these falsifications were contributed by the researchers who proposed the original hypotheses, and yet their later work has been ignored as the original speculation continues to be perpetuated as fact. In some cases, newer data clearly correct earlier plausible (but unsupported) hypotheses, but in others the contradictions remain to be resolved.

One often-repeated myth about naked mole-rats is the story that early European field biologists assumed them to be immature offspring of a haired adult (Jarvis & Bennett, 1991; Honeycutt, 1992; Park, Lewin, & Buffenstein, 2010) or to be diseased or decrepit (Bennett & Faulkes, 2000). In reality, Eduard Rüppell noticed their 'bald skin with the exception of single rows of long whitish hair' in his first description of the species (Rüppell, 1845, p. 100), mentioning that the hunter from whom he had received the individual reported the abundance of hairless and similar-sized specimens in several regions of Ethiopia. The myth that Rüppell thought that adult naked mole-rats had fur may derive from the illustration included in his monograph, in which the artist added fur to the specimen (Fig. 1).

Interest in naked mole-rats has increased dramatically over recent years (Figs. 2 and 3) because of their many unusual traits. Initially, their peculiar thermoregulatory adaptations received attention (McNab, 1966). In the 1980s and 1990s, the social behaviour of this species (Jarvis, 1981) was studied intensively. More recently, there is interest in naked mole-rats as a model for delayed senescence (Buffenstein & Jarvis, 2002; Buffenstein, 2005, 2008; Edrey *et al.*, 2011; Valenzano *et al.*, 2017; Ruby, Smith, & Buffenstein, 2018) and cancer resistance (Buffenstein, 2008; Delaney *et al.*, 2013, 2016; Shepard & Kissil, 2020). Consequently, this is an appropriate time for basic facts about this species to be comprehensively reviewed to avoid wasted research effort and resources.

II. ECOPHYSIOLOGY AND ENVIRONMENT

(1) Myth 1: naked mole-rats are hairless

Naked mole-rats have often been described as hairless (Kanui, Karim, & Towett, 1993; Browe, Vice, & Park, 2020), but their hair is simply very sparse. Tactile hairs are distributed all over their body and are most abundant on the face and tail. The longest hairs are facial whiskers (1–2 cm). Short and stiffer hairs border the mouth, eyelids, sides of the toes, and the outer edges of the hind feet. They display numerous eyelashes, and hairs and glands in the external acoustic meatus (Jarvis & Sherman, 2002). Naked mole-rats respond with highly predictable spatial reorientation (Crish *et al.*, 2003) upon tactile stimulation of the hairs dispersed over the body surface, indicating their importance for spatial orientation in the dark environment of subterranean burrows.

(2) Myth 2: naked mole-rats are strictly subterranean and never go above ground

Because of their apparent vulnerability due to poor eyesight and bare skin, it was assumed that naked mole-rats are never active above ground. This was supported by the lack of leaves and stems in the soft nests that the animals construct underground (Brett, 1991). However, the fact that most non-reproductive naked mole-rats in the wild are counter-shaded with a pigmented dorsum and pale ventrum (Braude *et al.*, 2001), led to the suggestion that there must be some above-ground activity. The discovery of a 'dispersal morph' (O'Riain, Jarvis, & Faulkes, 1996) captured above ground in pitfall traps (Braude *et al.*, 2020) and dispersal distances of more than 2 km (Braude, 2000) has corrected this misunderstanding. Thus, while there is no direct evidence of above-ground foraging, naked mole-rats do disperse above ground.

(3) Myth 3: naked mole-rats have unusually long burrows

Burrow systems of naked mole-rats were claimed to be the longest in absolute terms of all subterranean rodents

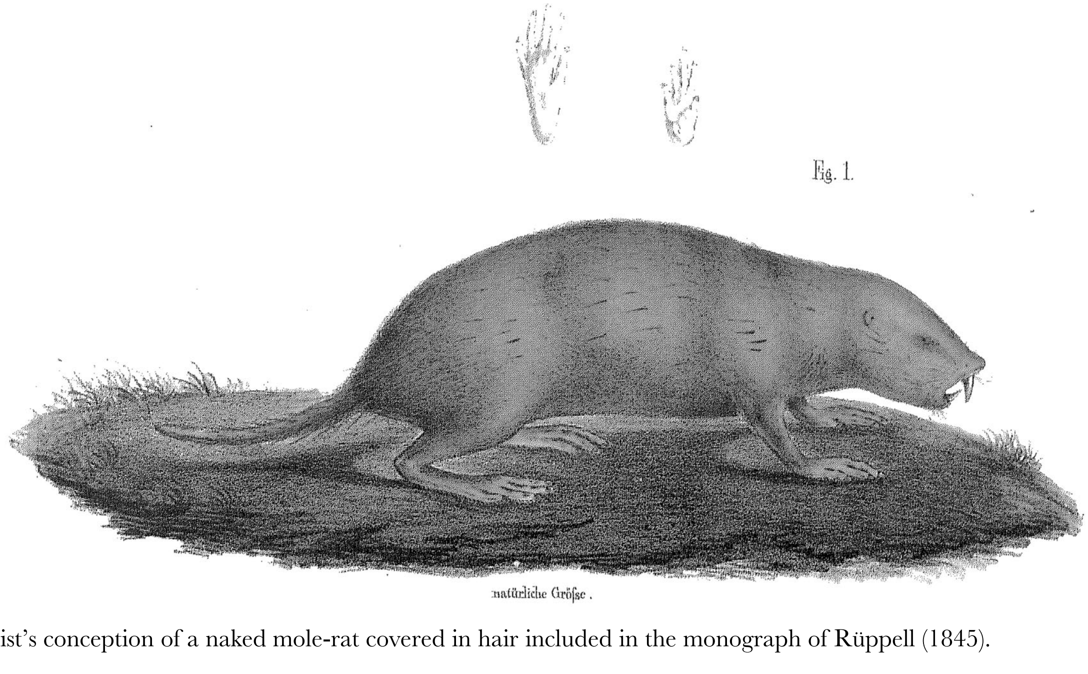

Fig 1. Artist's conception of a naked mole-rat covered in hair included in the monograph of Rüppell (1845).

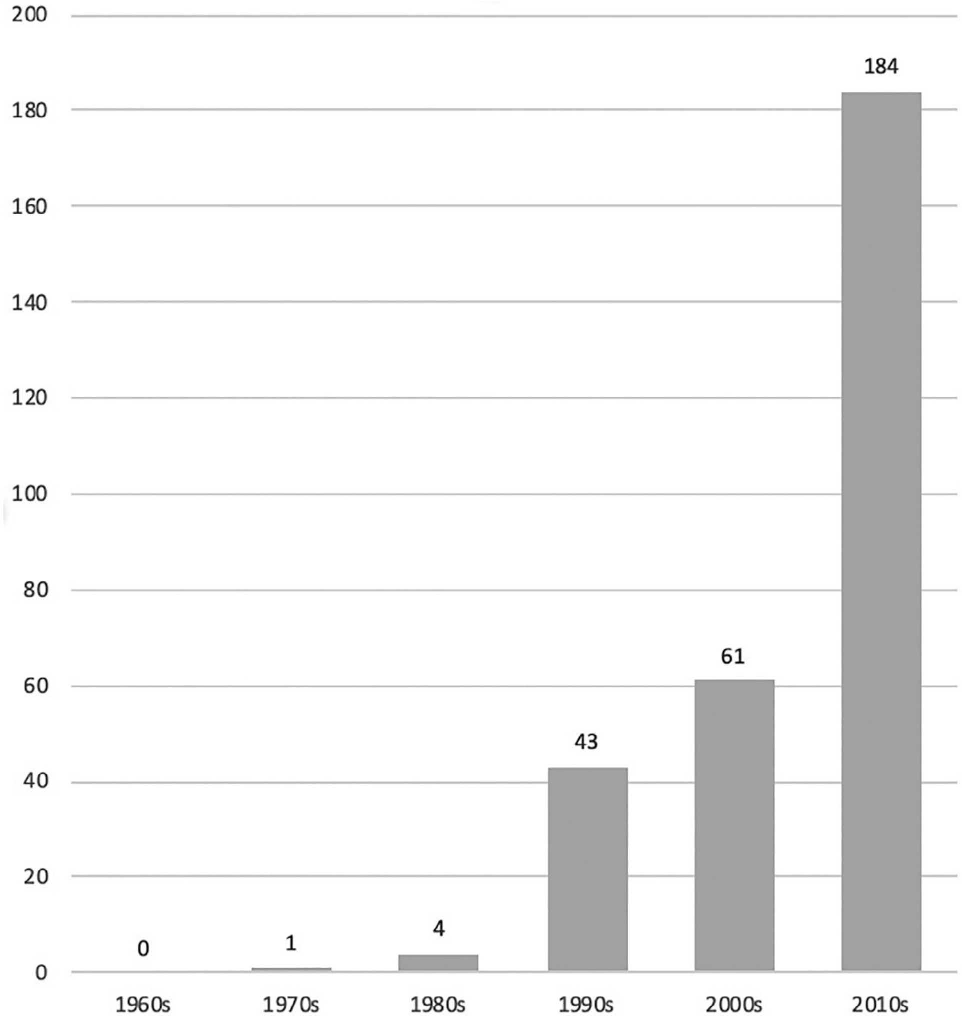

Fig 2. Number of publications with 'naked mole-rat' in the title, according to publication decade. The number of articles found by a search in *Google Scholar* are shown.

(3027 m estimated by Brett, 1991 using radiotelemetry and partial excavation, and 595 m uncovered by Jarvis, 1985). These equate to a ratio of naked mole-rat biomass to burrow system length of 1.1 and 2.1 g/m, respectively. This low ratio was considered to indicate harsh living conditions requiring extensive excavations to find sufficient randomly distributed

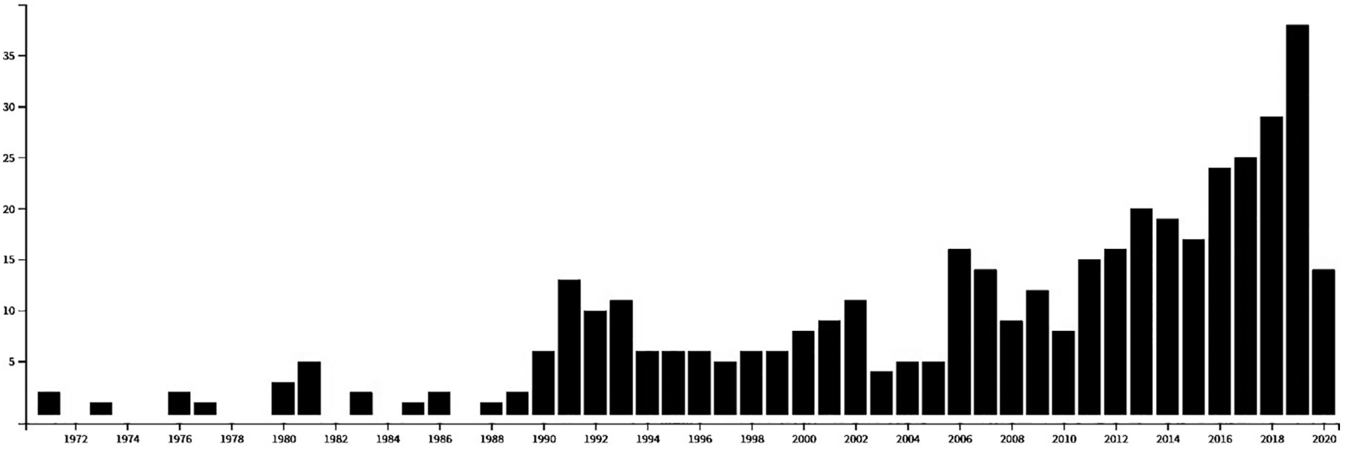

Fig 3. The number of citations per year with 'naked mole-rat' in the title.

geophytes. Despite subsequent evidence that the relative length of the burrow system in naked mole-rats was comparable with that of *Cryptomys* mole-rats and even with the solitary *Heliophobius* mole-rat (see Table 3–3 in Jarvis & Bennett, 1991), references to the extraordinarily long burrow systems of naked mole-rats remained in popular articles. Šumbera *et al.* (2012) uncovered two burrow systems of the giant mole-rat *Fukomys mechowii* with total lengths of 2245 and 743 m, making them the largest burrow systems ever mapped in relation to biomass. Comparable burrow system lengths were detected in the small-sized social bathyergid *Fukomys anselli* (Šklíba *et al.*, 2012), with a group biomass to burrow system length ratio of 0.4 g/m being the lowest recorded for any subterranean rodent.

(4) Myth 4: naked mole-rats are the only poikilothermic mammals

The naked mole-rat was initially considered to be a poorly thermoregulating endotherm, but still homeothermic because of their ability to regulate body temperature (T_b) by various means, i.e. by locating themselves appropriately to absorb or shed heat, or behaviourally thermoregulating by generating heat from muscle activity, or by huddling to conserve heat (Withers & Jarvis, 1980). It was subsequently described as the only example of an endothermic poikilotherm mammal, mainly based on its inability to regulate T_b across a broad ambient temperature (T_a) range and on a putative lack of non-shivering thermogenesis (Buffenstein & Yahav, 1991). Its T_b was found to be linearly correlated with T_a and generally only 0.6°C above T_a, although Buffenstein & Yahav (1991) stressed that the naked mole-rat does not experience a T_a below 28°C in their natural habitat, meaning that T_b would not fall below this value. It was later demonstrated that this species does possess non-shivering thermogenesis (Hislop & Buffenstein, 1994; Daly, Williams, & Buffenstein, 1997), and field data contradicted the assumption of a constantly high and stable T_a in its burrows (Holtze *et al.*, 2017). Although many studies on naked mole-rat thermoregulation support a strong dependency of T_b on T_a, they nevertheless maintain a higher T_b than their surroundings (McNab, 1966; Withers & Jarvis, 1980). Moreover, cold-acclimated naked mole-rats increase thyroid hormone production, basal metabolic rate and basal heat production, which are typical homeothermic acclimatization processes (Buffenstein *et al.*, 2001; Woodley & Buffenstein, 2002). Skin temperature immediately upon capture was shown to vary mostly within the species' thermoneutral zone despite a large temperature range inside the burrows (Holtze *et al.*, 2017). Gesser, Johansen, & Maloiy (1977) described naked mole-rat tissue metabolism as more typical of homeotherms than of poikilotherms. Various observations show that the naked mole-rat is able to avoid low T_b in many ways: *via* physical activity, moving to suitable microenvironments, the timing of activity, and non-shivering thermogenesis. The inability to maintain a stable T_b is mainly due to a small body size combined with efficient heat loss due to the lack of a subcutaneous fat layer and fur, resulting in an almost threefold higher conductance compared to other rodents of similar body mass (McNab, 1966; Withers & Jarvis, 1980). Thus, similar to other bathyergid species, they can be considered endothermic and partially homeothermic, although with a limited ability to maintain a stable T_b, but not poikilothermic.

(5) Myth 5: naked mole-rats have uniquely low thyroid hormone levels

Naked mole-rats are often described as hypothyroid, i.e. with low thyroid hormone (TH) levels compared to other mammals, especially in the context of ageing research (Buffenstein, 2005; Buffenstein & Pinto, 2009; Allard & Duan, 2011; Lewis, Rubinstein, & Buffenstein, 2018; Gan *et al.*, 2019). The THs triiodothyronine (T3) and its precursor thyroxine (T4) are central regulators of energy metabolism and thermoregulation. In mammals, low TH levels are associated with the downregulation of metabolic rate and T_b as well as extended lifespan (Allard & Duan, 2011; Mullur, Liu, & Brent, 2014). Naked mole-rats, along with other bathyergids, have a very low resting metabolic rate (RMR) and low T_b compared to similar-sized rodents, which may represent an ecophysiological adaptation to a subterranean habitat (McNab, 1966; Johansen *et al.*, 1976; Zelová *et al.*, 2007). Buffenstein *et al.* (2001) reported extremely low levels of T4 in naked mole-rats, resembling reptilian rather than mammalian levels (Anderson, Nixon, & Akasha, 1988; Hulbert & Williams, 1988). However, levels of T3, which is the receptor-active hormone responsible for TH-dependent gene expression, were not measured but rather inferred from T4 levels. According to a press release from the American Physiological Society (2006), T3 levels of naked mole-rats were found to be similar to those of mice and Damaraland mole-rats (*F. damarensis*). However, in the publication to which this press release referred, T3 levels of naked mole-rats were not reported and TH levels were described as generally low (Buffenstein & Pinto, 2009). Recently, a comprehensive analysis of TH levels in another bathyergid, Ansell's mole-rat (*F. anselli*), revealed that while T4 levels were low, circulating T3 levels were in a rodent-typical range (Henning *et al.*, 2014). The resulting T4:T3 ratio is unique among mammals (Anderson *et al.*, 1988) and remains puzzling biologically because these T3 levels should be sufficient to upregulate TH-dependent parameters such as RMR and T_b. Thus, naked mole-rats do not have uniquely low TH levels compared to other mammals, but together with other bathyergids appear to have a completely different TH physiology. Further research will be necessary to understand the proximate and ultimate mechanisms involved.

(6) Myth 6: naked mole-rat burrows are hypoxic and hypercapnic

Larson & Park (2009) and Park *et al.* (2017) cite McNab (1966) as the source of the popular belief that naked mole-rat burrows are hypercapnic. Park *et al.* (2017, p. 307) specificially claim that 'CO_2 levels in naked mole-rat burrows can reach 7 to 10%, orders of magnitude higher than in surface air.' However, McNab was unable to provide supporting data because the naked mole-rats 'vandalized' his sensors (McNab, 1966, p. 715). Kim *et al.* (2011) cite Bennett & Faulkes (2000) as the source for hypoxic (8% O_2) and hypercapnic (>10% CO_2) burrows, but these values do not appear in the cited book. Hypoxia and hypercapnia might be expected in a sealed burrow containing respiring animals and plant roots, although this is not supported by measurements in naked mole-rat burrows (Holtze *et al.*, 2017) nor in the burrows of other bathyergids (Roper *et al.*, 2001; Šumbera *et al.*, 2004; Šumbera, 2019). However, naked mole-rats can tolerate extreme hypoxia, even anoxia (Larson & Park, 2009; Pamenter, Dzal, & Milsom, 2015; Park *et al.*, 2017) and show hypoxia- and hypercapnia-related adaptations (e.g. Peterson *et al.*, 2012; Branigan, Elkhalifa, & Pamenter, 2018). When naked mole-rats huddle together in their nests, the animals at the bottom of the pile experience extreme hypoxia (e.g. Park *et al.*, 2017; Zions *et al.*, 2020) to the extent that they can lose consciousness and may take up to 15 min to recover when they are moved to a normoxic environment (S. Braude & S. Holtze, personal observations).

III. SENSORY ECOLOGY

(1) Naked mole-rats are blind

The eye of the naked mole-rat is relatively small; however, the optical apparatus, including the retina, contains all structures of a typical mammalian eye (Peichl, Němec, & Burda, 2004). The lens is large in relation to eye size (Nikitina *et al.*, 2004), perhaps to enhance close focus *versus* distance vision. The retina is normally developed and possesses all characteristic layers. The photoreceptor layer is dominated by rods but contains an unusually high proportion of cones (approximately 10%), which solely express S-opsins (Peichl *et al.*, 2004; Kim *et al.*, 2011). Thus, the naked mole-rat is the only known mammalian S-opsin monochromat. Rod density is lower than in surface-dwelling rodents, and individual rods are larger (Peichl *et al.*, 2004). Other retinal neuron types are present but are less organized than in surface-dwelling rodents (Mills & Catania, 2004). The optical nerve is thin compared to that of the gerbil (*Meriones unguiculatus*) (Hetling *et al.*, 2005). Subcortical visual nuclei are smaller except for the suprachiasmatic nucleus (Němec *et al.*, 2008). The optical pretectal nucleus, which functions as a luminance detector, is rather well developed (Crish, Dengler-Crish, & Catania, 2006). The visual cortex is reduced at the expense of the somatosensory cortex (Catania & Remple, 2002; Henry *et al.*, 2006). Nevertheless, the naked mole-rat is not blind, since the retina reacts to bright light flashes and the animals avoid light directed towards their nest chamber (Hetling *et al.*, 2005).

(2) Myth 8: naked mole-rats have degenerated hearing

Behavioural tests of absolute sensitivity and sound localization in naked mole-rats show that their ability to detect sound is limited, with a maximum sensitivity of only 35 dB at 4 kHz. Their high-frequency hearing is severely limited, with their hearing range at 60 dB sound pressure extending from 65 Hz to only 12.8 kHz. Determination of the effect of duration on noise thresholds indicates that, compared with other animals, naked mole-rats require a sound to be present for a much longer period before reaching an asymptotic threshold. Finally, they are unable consistently to localize sounds shorter than 400 ms and cannot accurately localize sounds of longer duration (Heffner & Heffner, 1993). The latter authors described these features as degenerate, arising due to a lack of acoustic stimulation in subterranean burrows and thus low selection for hearing ability. Comparable hearing characteristics are found in other subterranean rodents (reviewed in Begall *et al.*, 2007). Hearing in subterranean rodents generally matches the acoustics in burrows (Heth, Frankenberg, & Nevo, 1986; Lange *et al.*, 2007), in that it is not responsive to high frequencies (potentially due to lack of stimulation). However, the hearing range (in terms of octaves) tends not to be reduced but instead is shifted towards the lower frequencies that are transmitted best in burrows. Hearing sensitivity in the lower frequency range is thus conserved or even improved relative to above-ground rodents such as rats. This reduction of peak hearing sensitivity may allow compensation for the amplification of sounds by a 'stethoscope effect' in tunnels (Lange *et al.*, 2007). The similar middle ear morphologies of many subterranean rodents, and of the guinea-pig (*Cavia porcellus*), are consistent with tuning to low frequencies (reviewed in Begall *et al.*, 2007): none of the components of the middle ear are reduced or degenerated, in fact some parts, particularly the incus and the stapedial footplate, are enlarged, leading to better sensitivity to low frequencies. Based on cochlear measurements (see Table 3 in Mason, Cornwall, & Smith, 2016), the radius ratio for naked mole-rats is 3.84 and the product of basilar membrane length by spiral turns is 15.9. Thus, similar to other subterranean mammals, naked mole-rats are shifted to better low-frequency hearing compared with expected values for a typical rodent of similar size (see Figs 2 and 3 in Mannoussaki *et al.*, 2008).

(3) Myth 9: naked mole-rats are the most vocal rodents because they live in large groups

Sherman, Jarvis & Braude (1992, p. 76) stated that 'The mole rat's vocal repertoire is the most extensive known among rodents and rivals that of some primates in its richness.' It is generally expected that vocal-repertoire size correlates positively with group size (e.g. McComb & Semple, 2005). It is thus not surprising that with an average colony size of 78 individuals (Sherman *et al.*, 1992) and 17 different vocalizations (Pepper, Braude, & Lacey, 1991), the naked mole-rat has been frequently described as the rodent with the largest vocal repertoire (Sherman *et al.*, 1992; Bennett & Faulkes, 2000; Yosida *et al.*, 2007; Vaughan, Ryan, & Czaplewski, 2013; Toor *et al.*, 2015). However, the 17 vocalizations described by Pepper *et al.* (1991) included five pup vocalizations. Recent studies on the genus *Fukomys* show that many *Fukomys* species with much smaller mean family sizes (7–12 individuals) have a similarly rich adult repertoire compared to that of the naked mole-rat (13 vocalizations in the Ansell's mole-rat *Fukomys anselli*; 11 in the Mashona mole-rat *F. darlingi*; 10 in the Micklem's mole-rat *F. micklemi*) [see Dvořáková, Hrouzková, & Šumbera, 2016 for an overview]. The largest social bathyergid, the giant mole-rat *F. mechowii*, possesses an even larger diversity of vocalizations, including 16 adult sounds (Bednářová *et al.*, 2013). Thus, the richness of the vocal repertoire in African mole-rats may be influenced by factors such as social complexity and stability, rather than merely group size. It is possible that naked mole-rat colonies, although numerically the largest, are less socially complex as a result of the large group size and large turnover due to high fecundity and dispersal mortality [see Burda *et al.*, 2000 for comparison of family dynamics and turnover in the genera *Heterocephalus* and *Fukomys*].

(4) Myth 10: naked mole-rats feel no pain

Park *et al.* (2008) explored inflammatory hyperalgesia in naked mole-rats because they were known to lack calcitonin gene-related peptide (CGRP) and substance P in cutaneous sensory C-fibres involved in pain transmission. Although naked mole-rats are insensitive to acid, their sensory neurons do respond to capsaicin (Park *et al.*, 2008) and histamine (Smith *et al.*, 2010). However, the afferent signal to both of these is blocked at the dorsal root, and neither hyperalgesic thermal sensitivity nor scratching behaviours are expressed. Nonetheless, contrary to Browe *et al.* (2020) and Griffin (2008), naked mole-rats can sense pain *via* Aδ fibers, and respond normally to tissue damage (S. Braude, T.B. Hildebrandt & S. Holtze, personal observations).

IV. SOCIAL BEHAVIOUR AND REPRODUCTION

(1) Myth 11: naked mole-rats are the only eusocial mammals

The naked mole-rat was the first mammal species to be described as eusocial (Jarvis, 1981) but the misconception that it is the only eusocial mammal has persisted in the literature (Hetling *et al.*, 2005; O'Riain & Faulkes, 2008; Johnstone & Cant, 2019), despite clear evidence to the contrary. By 1988, at least one further species in the family Bathyergidae, *Fukomys damarensis*, was described as eusocial (Bennett & Jarvis, 1988). Eusociality in mole-rats has been considered necessary for cooperative foraging in hostile environments with widely dispersed food resources (the Aridity–Food Distribution Hypothesis; Jarvis *et al.*, 1994) or to result from predation pressure by specialized snakes in the subterranean ecotope (Alexander, 1991; Alexander, Noonan, & Crespi, 1991). However, there is no evidence for a common selective force leading to sociality when we consider the spectrum of social fossorial rodents, including the ctenomyids (Lacey & Weizorek, 2003). Indeed, sociality is more common among above-ground mammals than in subterranean species and is independent of habitat aridity and available resources (Burda, 1999; Burda *et al.*, 2000; Lövy *et al.*, 2012; Šklíba *et al.*, 2012; Šumbera *et al.*, 2012).

Eusociality was initially excluded for other members of Bathyergidae due to their smaller colony sizes (Jarvis & Bennett, 1993). Here we must consider what is meant by the term 'colony'. Groups of naked mole-rats and Damara mole-rats used to be called colonies in the literature, in analogy with social insects. We use this term here as well, yet it should be clear that in vertebrates, a colony typically designates an aggregation of solitary, though gregarious, individuals (e.g. a breeding colony of gulls or seals, a colony of ground squirrels, etc.). A more appropriate term to describe the social system of mole-rats would be 'family'. Burda *et al.* (2000) argued that group size should not be used as a criterion for mammalian eusociality. In their view, reproductive altruism, an overlap of adult generations, and prevailing permanent (lifelong) philopatry of most offspring are the biologically relevant criteria. Accordingly, many of the other social species in the Bathyergidae (particularly many species of the genus *Fukomys*) should be considered eusocial.

(2) Myth 12: colonies have castes of breeders and non-breeders, involving frequent workers, infrequent workers, non-workers, and dispersers

The term 'caste' is defined for eusocial insects as a set of individuals performing specialized labour in the colony and belonging to a specific morphological type, age group or both (Wilson, 1975). A division and succession of specialization related to age (age polyethism; Wilson, 1971) in mole-rats was proposed by Jarvis (1981, p. 572): after weaning, all naked mole-rats rats become 'frequent workers' involved in burrow maintenance; fast-growing individuals then gradually develop into 'infrequent workers' and may finally become large 'non-workers' (Jarvis, 1981; Faulkes *et al.*, 1991b) who care for the young and may replace breeders.

There are obvious differences between reproductives and non-reproductives: reproductive females (queens) display lumbar vertebral elongation, resulting in distinctly different body proportions (Henry, Dengler-Crish & Catania, 2007; O'Riain *et al.*, 1996; Dengler-Crish & Catania, 2007). Additional but reversible morphological changes comprise increased gonad size and distinct morphology compared to workers in both female breeders, queens (Kayanja & Jarvis, 1971; Jarvis, 1981), and male breeders, pashas (Faulkes, Abbott & Jarvis, 1991*a*; Faulkes *et al.*, 1994). Males usually lose body mass after becoming breeders (Jarvis, O'Riain, & McDaid, 1991). Dispersers are characterized by large fat deposits and high levels of luteinizing hormone (LH) (O'Riain *et al.*, 1996). Reproductive animals (breeders), dispersers, and workers also differ behaviourally (Jarvis, 1991; Lacey & Sherman, 1991; Faulkes *et al.*, 1991b; O'Riain *et al.*, 1996). Breeders perform sexual behaviours and care for the offspring, rarely taking part in colony maintenance or risky tasks (Lacey & Sherman, 1991; O'Riain *et al.*, 1996). Most non-breeders are active around the clock, but dispersers display a nocturnal activity pattern (Riccio & Goldman, 2000) and disposition to leave the burrow. Behavioural differences among non-breeders are correlated with size and thus presumably with age (Jarvis, 1981, 1991; Faulkes *et al.*, 1991b). Differential patterns in neuronal reactivity to oxytocin have been observed in workers engaged in colony defence *versus* workers performing prosocial behaviours (Hathaway *et al.*, 2016). However, body mass development and growth are highly dynamic and not related linearly to age, allowing the colony to respond flexibly to changes in social structure (Jarvis, 1981; Jarvis *et al.*, 1991; Lacey & Sherman, 1991). Given their large behavioural variability and flexibility (e.g. after the removal of individuals), the existence of discrete castes among non-breeders is doubtful (Lacey & Sherman, 1991, 1997; Mooney *et al.*, 2015). Extensive research demonstrates that the eusocial *F. damarensis* does not differ from other cooperative vertebrates in terms of task specialization (Zöttl *et al.*, 2016; Thorley *et al.*, 2018). Thorley *et al.* (2018, p. 9) even argue that 'unequivocal evidence of caste differentiation in any cooperative vertebrate' is doubtful and that we should be cautious about interpreting these differences among categories of animals as 'castes'. Despite the inherent difficulty of observing animals underground in the wild, we also need to be wary of behaviour observed only in extremely artificial laboratory conditions.

(3) Myth 13: colonies have up to three male breeders (pashas)

All cooperatively breeding mammals have been assumed to arise from monogamous ancestors, and cooperative breeding without monogamy appears to be unstable (Lukas & Clutton-Brock, 2012). Due to their harsh environment and high mortality risk of dispersal, the kin selection model predicts a benefit for naked mole-rat offspring to remain in the natal colony and help their parents raise full siblings (Bourke, 2014). It is thus surprising that some observers have described up to three males to be involved in reproduction in a single colony (Jarvis, 1991; Jarvis *et al.*, 1991; Lacey & Sherman, 1991; Faulkes, Abbott, & Jarvis, 1991a). This conclusion was based on observations of 14 captive colonies, of which three were described as having three breeding males, three others had two breeding males and the remaining eight had a single breeding male. Reeve & Sherman (1991) even reported one colony with four breeding males. However, these behavioural studies refer to 'mating males' as 'reproductive males' without assessing paternity. Lacey *et al.* (1991) describe three different mating behaviours: backing, mounting, and copulating. In their definition of 'copulation', Lacey *et al.* (1991) note the occurrence of 'pelvic thrusting' as opposed to mere 'mounting attempts', whereas thrusting was not mentioned by Jarvis *et al.* (1991) despite its potential importance for the accurate identification of reproductive males. While most authors simply refer to 'mating' some have identified male breeders solely based on anogenital interactions, which is even more unreliable as it may also occur with and among non-breeders (Jarvis, 1991). However, DNA fingerprint studies have shown that two fathers were represented in two litters of a captive colony (Faulkes *et al.*, 1997), and multiple fathers were reported for one wild colony (Braude, Hess, & Ingram, in press). K. Szafranski (unpublished data) tested four captive colonies and found evidence of only one father per colony. Further paternity analyses are urgently needed to describe the mating system accurately in wild colonies. As opposed to *F. anselli* (Garcia Montero *et al.*, 2016), non-breeding male naked mole-rats show reduced testis size and decreased sperm quality compared to breeders, indicating restriction of male reproduction potential (Faulkes *et al.*, 1991a, 1994).

(4) Myth 14: colonies have a single queen

Although it is frequently reported in the literature that naked mole-rat colonies contain only one breeding female or queen (e.g. Faulkes & Abbott, 1993; Menon *et al.*, 2019; Browe *et al.*, 2020), there is evidence from both captive and wild colonies that more than one breeding female may be present (Jarvis, 1991; Jarvis *et al.*, 1991; Clarke & Faulkes, 1997; T.B. Hildebrandt & S. Holtze, personal observations). Among eight cases of parallel queens in the laboratory reported by Jarvis *et al.* (1991), seven colonies temporarily contained two, and one colony even had three breeding females. This is most often seen when an established queen dies or is removed, and more than one daughter begins to develop reproductively; tolerance of a second reproductive female by her mother is less common (Jarvis, 1991). The presence of two breeding females typically leads to fighting, mortality, and a significant decline in pup survival (Jarvis, 1991). It usually is of short duration, although one case has been reported to last for more than 5 years. Colonies with two queens have been observed in the wild. In both cases, a daughter was tolerated alongside her mother. In one of these cases, the two produced litters together for more than a year (S. Braude, personal observations).

(5) Myth 15: not all females can become queens

Jarvis (1981, p. 572) suggested that the ability of female naked mole-rats to reproduce is retained only for a limited portion of their lives, after which they can be described as being in 'menopause'. Unlike queens, non-reproductive females have quiescent ovaries (Kayanja & Jarvis, 1971), low circulating levels of LH, and no cyclical changes in circulating progesterone levels (Faulkes, Abbott, & Jarvis, 1990a) indicating an absence of ovulation. The queen exerts physical stress (shoving and biting) on her subordinates, which is thought to impair hypothalamic gonadotropin-releasing hormone (GnRH) secretion (Faulkes *et al.*, 1990b). This ovulatory block is reversible within approximately eight days after removal or death of a queen, or if non-reproductive females are housed without physical contact with the queen (Faulkes & Abbott, 1993; Smith, Faulkes, & Abbott, 1997). In the former case, the next most dominant or heavy females usually fight for succession (Clarke & Faulkes, 1997). Queen succession within an established colony or when pairing workers may take between one week and 24 months (mean 5 months, $N = 27$), i.e. the time until the new queen conceives her first litter (T.B. Hildebrandt & S. Holtze, personal observations). A non-breeding female paired with a non-breeding male may start breeding (e.g. Jarvis, 1991; Jarvis *et al.*, 1991; Faulkes *et al.*, 1991b, 1997), with recorded success rates of 73% ($N = 40$ over 1 year; Yu *et al.*, 2017), 75% ($N = 4$ over 2.5 years; Henry, Dengler-Crish, & Catania, 2007), and 100% ($N = 10$ over 2.2 years, T.B. Hildebrandt & S. Holtze, personal observations). Females as young as eight months ($N = 2$; T.B. Hildebrandt & S. Holtze, personal observations) and as old as 16 years (Buffenstein, 2005) have developed into queens and given birth for the first time. Some females may fail to breed due to incompatibility, compromised reproductive health, or suboptimal husbandry conditions. Thus, not all naked mole-rat females retain the option to become a queen for their entire lives. However, unlike female termite workers, most naked mole-rat females are physiologically able to develop into queens.

(6) Myth 16: queens suppress workers with pheromones

Jarvis (1981) initially speculated that pheromones might be the mechanism of worker suppression. Faulkes *et al.* (1990a) showed, however, that suppression was socially imposed, as in dwarf mongoose (*Helogale parvula*), jackal (*Canis mesomelas*), marmoset (*Callithrix jacchus*), and tamarin (*Saguinus imperator*). Watarai *et al.* (2018) fed queen faeces to non-breeders and found that this increased oestradiol levels and responses to pup vocalizations and alloparental behaviour in those workers. However, there is no evidence that naked mole-rat non-breeders ever consume queen faeces either in the wild or the laboratory setting. None of the co-authors of this review have observed this behaviour in our thousands of hours of laboratory observations.

(7) Myth 17: queens shove workers to get them to work

Reeve (1992) proposed that shoving behaviour is directed against workers in order to encourage them to work rather than as a means of reproductive suppression. Shoving behaviour in captive colonies was first described by Lacey *et al.* (1991) and Reeve & Sherman (1991). These two functions, encouragement to work and reproductive suppression, are not mutually exclusive, but the rate of shoving declined when more work was needed: 'the queen's total rate of shoving significantly declined with increased food deprivation interval' (Reeve, 1992, p. 148). Furthermore, chewing on the walls of the tunnels and digging were included in the behaviours categorized as work, but both may instead represent dispersive effort. Nonetheless, Jacobs & Jarvis (1996) reported no change in work levels after shoving. This behaviour clearly deserves further observation in colonies required to dig in order to access food and from which dispersers can freely escape.

(8) Myth 18: naked mole-rats never leave their natal colonies

After a long period of repudiating the ability of naked mole-rats to disperse successfully, a dispersive morph was discovered and described by O'Riain *et al.* (1996). The dispersal phenotype is morphologically, behaviourally and physiologically distinct from other colony members. Dispersers have brown adipose tissue on the cranial dorsum, exhibit elevated levels of active blood plasma LH, are more likely to run, and solicit mating with individuals from other colonies. Ciszek (2000) demonstrated that naked mole-rats tend to prefer outbreeding, and storage of fat in dispersing animals is relatively common in mammals. O'Riain *et al.* (1996) found that these dispersal characteristics closely parallel those seen in founders of ant and termite colonies, but noted their relatively low occurrence (less than 2%) in their population of laboratory animals. Burda (1999) critically reassessed their data and found that in older families (more than 4 years) the number of such dispersers was higher, reaching 27% of all non-breeding males.

(9) Myth 19: naked mole-rats are inbred

The idea that naked mole-rats are inbred is appealing because it is linked with an elegant genetic explanation for their unusual social behaviour (e.g. Legese & Bekele, 2019; Salgotra & Singh, 2019). As summarized by Sherman *et al.* (1992, p. 78): 'Because of inbreeding, siblings are extremely closely related, and thus, as noted by Hamilton for eusocial Hymenoptera, a worker mole-rat reaps genetic returns for helping them.' Others suggested that as a result of inbreeding, deleterious alleles have been eliminated (Ross-Gillespie, O'Riain, & Keller, 2007; Aviles & Purcell, 2012). The first evidence of inbreeding came from low heterozygosity in captive colonies and DNA fingerprint data of naked mole-rats mostly captured in southern Kenya (Reeve *et al.*, 1990). However, these animals came from a recent bottlenecked population that only crossed the Athi river 100 years earlier (Jarvis, 1985), meaning that the reported inbreeding was the result of genetic drift rather than the system of mating. Consistent with Burda (1995), Clarke & Faulkes (1999) found that queens prefer to mate with unrelated males, and Ciszek (2000) demonstrated that naked mole-rats avoid mating with siblings. Ciszek (2000) isolated groups of four individuals made up of two different pairs of male and female siblings. None of the resulting breeding pairs included siblings. Ingram *et al.* (2015) examined the genetic landscape of dozens of naked mole-rat colonies from across Kenya and found no evidence of inbreeding north of the Athi River. Hence, naked mole-rats have not evolved under ecologically imposed inbreeding but will tolerate inbreeding in the wild and the laboratory.

V. DEVELOPMENT, LONGEVITY, AGEING AND SENESCENCE

(1) Myth 20: the GH/IGF axis is impaired in naked mole-rats

Mouse models with defects in the growth hormone(GH)/ insulin-like growth factor (IGF) axis are often long lived (Junnila *et al.*, 2013). Brohus *et al.* (2015) speculated that phenotypic traits of naked mole-rats might suggest impaired GH/IGF-signalling. *In vitro*, naked mole-rat fibroblasts produce a protease that rapidly degrades IGF binding protein (IGFBP)-4 and -5, but not IGFBP-3 (Brohus *et al.*, 2015). However, there is no direct evidence for impairment of the GH/IGF axis in naked mole-rats. In fact, hepatic expression of IGF-2 and IGF-1 receptor messenger RNA (mRNA) is higher in naked mole-rats than in the mouse or rat (Fang *et al.*, 2014*b*).

(2) Myth 21: naked mole-rats are long-lived because they have low oxidative stress and damage

The oxidative stress theory states that accumulation of oxidative damage [due to an imbalance between the production of and defence against reactive oxygen species (ROS)] causes ageing (Miwa, Muller, & Beckman, 2008). Unexpectedly, higher levels of oxidative modifications to lipids (Andziak & Buffenstein, 2006; Edrey *et al.*, 2014), proteins (Andziak *et al.*, 2006; Perez *et al.*, 2009), and DNA (Andziak *et al.*, 2006) have been measured in urine and various tissues of the naked mole-rat than in those of mice, contradicting the prediction of low levels of oxidative damage in longer-lived animals. At the protein level, severe damage to the important glycolytic enzyme triosephosphate isomerase (TPI) in the renal tissue of naked mole-rats was observed, although with no impairment of the activity of this enzyme being detected (Andziak *et al.*, 2006). Significantly reduced glutathione (GSH) levels and a reduced ratio of GSH to glutathione disulphide (GSSG; an important cellular antioxidant), accompanied by 10-fold higher levels of *in vivo* lipid peroxidation (Andziak & Buffenstein, 2006) also do not fit with the hypothesized enhanced resistance to oxidative damage. Naked mole-rat heart muscle mitochondria release as much H_2O_2 as those of mice (Munro *et al.*, 2019). This makes them an outlier relative to the inverse relationship between maximum lifespan and H_2O_2 release of isolated heart mitochondria established in other vertebrates, independent of body mass or phylogeny (Lambert *et al.*, 2007). Naked mole-rat mitochondria release far more ROS than expected for their longevity, although this rate of release remains constant over their lifespan (Andziak & Buffenstein, 2006). There are other exceptions to this inverse relationship, most prominently humans: human muscle mitochondria ROS production approximates that of mice (Abdul-Ghani *et al.*, 2009; Lefort *et al.*, 2010). Both in humans and naked mole-rats, genes encoding nuclear DNA repair enzymes, and most DNA-repair signalling pathways are expressed at higher levels than in mice (MacRae *et al.*, 2015). The naked mole-rat liver, an organ exposed to a large number of DNA-damaging agents, shows strong over-expression of genes associated with oxidoreduction, detoxification and mitochondria compared to mouse liver (Yu *et al.*, 2011). This is reflected in proteomic signatures (Heinze *et al.*, 2018) and positively selected genes (Sahm *et al.*, 2018), as well as the accumulation of genes involved in DNA repair in naked mole-rats. Thus, in the liver of naked mole-rats more DNA-repair genes are expressed for the recognition of DNA damage [such as tumor suppressor TP53, DNA mismatch repair proteins or non-homologous end joining (NHEJ) repair proteins] than in mice, implying better genome care in these rodents (MacRae *et al.*, 2015). However, genes for DNA glycosylases, which are essential for the removal and replacement of damaged DNA bases (O'Brien, 2006), and polymerases, which are involved in cell cycle progression (Zucca *et al.*, 2013) and translation synthesis (Haracska, Prakash, & Prakash, 2002), are also more strongly expressed in naked mole-rats and in humans than in mice (MacRae *et al.*, 2015). Yu *et al.* (2011) found overexpression in naked mole-rats of the subunit c (Sdhc) of the succinate dehydrogenase complex, a member of the tricarboxylic acid (TCA) cycle and the mitochondrial electron transport chain and known to be a major source of ROS production (revised in Dröse, 2013). Sdhc overexpression could be associated with higher levels of ROS (Andziak & Buffenstein, 2006) and of oxidative damage to lipids, DNA, and proteins (Andziak *et al.*, 2006), reflecting a greater need for protection against ROS. Yu *et al.* (2011) also found overexpressed genes in fatty acid metabolism and lipid biosynthesis, linking this to the correlation between membrane fatty acid composition and maximum mammalian lifespan expectancy by reducing oxidative damage due to lipid peroxidation (Hulbert, 2008).

A comparison of ROS formation in vessels of naked mole-rats and mice (Labinskyy *et al.*, 2006) or rats (Csiszar *et al.*, 2007) suggests that the endothelial vasodilator function and vascular production of ROS do not correlate with maximum lifespan. However, the comparison suggests that increased lifespan may be associated with increased vascular resistance to proapoptotic factors. Furthermore, the observed reduction in 'canonical' antioxidant systems in naked mole-rats may be compensated by other specific mechanisms. For example, docosahexaenoic acid (DHA), an n-3 polyunsaturated fatty acid, is very susceptible to lipid peroxidation and is nine times lower in naked mole-rat cellular membranes compared to those of mice (Hulbert, Faulks, & Buffenstein, 2006). Although mitochondrial oxygen consumption in naked mole-rats is 2–5-fold higher than in mice, isolated naked mole-rat mitochondria were able to detoxify significantly more ROS *via* their antioxidative systems (Munro *et al.*, 2019). Another mechanism of ROS detoxification is mediated by mild depolarization *via* mitochondrial membrane-bound hexokinases I and II; their expression does not decline with age in long-lived naked mole-rats and bats in contrast to short-lived mice (Vyssokikh *et al.*, 2020). Finally, several recent studies postulate that long-lived species such as birds, bats and naked mole-rats exhibit high-levels of oxidative damage at a young age (reviewed in Buffenstein *et al.*, 2008), which can prime animals for high tolerance to ROS throughout life (Saldmann *et al.*, 2019).

Assuming oxidative stress and damage inevitably to result in premature ageing and age-related diseases disregards the ability of different species to maintain cellular integrity in the long term despite high levels of oxidative stress. Studies on the long-lived naked mole-rat continue to contribute to investigating and extending the oxidative stress theory of ageing.

(3) Myth 22: naked mole-rat cells do not display cellular senescence

Cellular senescence refers to a state of stable cell cycle arrest. Different stress responses leading to senescence of cells, including critical telomere shortening, have been described. Cellular senescence is believed to influence different physiological and pathological processes, including age-related diseases. However, its contribution to longevity or healthy ageing is still unclear. Therefore, research on cellular senescence using the naked mole-rat as a model species for longevity is of great interest.

Shekhidem *et al.* (2019) found the relative telomere length in circulating leukocyte DNA to decline with age in mice but not in naked mole-rats, suggesting that lack of proliferative senescence might be one mechanism by which lifespan is increased in naked mole-rats. Somatic cells of the mole-rat show telomerase activity and lack significant shortening of telomeres *in vitro* (Seluanov *et al.*, 2007). However, similar *in vitro* observations have been obtained for mice, which have a significantly shorter lifespan. There is clearly not a simple correlation between telomerase activity in somatic cells and lifespan. Fibroblasts from naked mole-rats, but also mice, did not show telomere-shortening-driven proliferative senescence *in vitro*. However, this senescence-resistant characteristic was observed only under specific culture conditions (32°C and 3% oxygen; Seluanov *et al.*, 2008). Under 20% oxygen, murine fibroblasts indeed displayed proliferative senescence *in vitro*, possibly due to an induced DNA-damage response, while naked mole-rat cells have been reported to display increased resistance to oxidative stress in other cellular systems (Parrinello *et al.*, 2013; Saldmann *et al.*, 2019).

Further studies in different tissues of the naked mole-rat are needed to clarify the relationship between changes in telomerase activity and longevity. Zhao *et al.* (2018) showed that naked mole-rat cells undergo developmentally programmed cellular senescence during embryogenesis. Naked mole-rat skin fibroblast cells underwent DNA-damage-induced senescence after γ-irradiation, although interestingly, a higher irradiation dose was needed to induce senescence. Naked mole-rat cells also were more resistant to apoptosis compared to mouse fibroblasts. Furthermore, Zhao *et al.* (2018) showed that oncogene-induced senescence could be induced after Rat sarcoma (Ras) overexpression. While single reports imply that naked mole-rat cells are more resistant to senescence, the data indicate that the molecular machinery for senescence induction is present. Whether senescent cells accumulate in the naked mole-rat with age or not remains an open question.

(4) Myth 23: naked mole-rats are immune to disease

Naked mole-rats have a remarkably low incidence of typical age-related diseases such as sarcopenia (O'Connor *et al.*, 2002; Stoll *et al.*, 2016), osteoporosis (Buffenstein *et al.*, 1994), and cancer (Buffenstein, 2008). Naked mole-rats effectively control and shape their microbiome (Debebe *et al.*, 2016), probably due to a highly developed myeloid compartment of the immune system (Cheng *et al.*, 2017;Hilton *et al.*, 2019; Shebzukhov *et al.*, 2019) and expression of cathelicidin-like protein with antibacterial activity (Cho *et al.*, 2018). Adult individuals are rarely found to be ill, both in the wild (Hill *et al.*, 1957) and under laboratory conditions (Buffenstein, 2008). This is confirmed by observations on more than 300 animals over 10 years at the Leibniz Institute for Zoo and Wildlife Research (IZW) (T.B. Hildebrandt & S. Holtze, personal observations) and also for several *Fukomys* species studied by S. Begall and P. Dammann at the University of Duisburg-Essen and R. Sumbera at the South Bohemian University.

However, naked mole-rats are susceptible to viral infections (Ross-Gillespie *et al.*, 2007; Artwohl *et al.*, 2009) and intracellular parasites such as *Leishmania donovani* (Githure, Gardener, & Kinoti, 1988). This is in accordance with the observation that the immune system of naked mole-rats has a relatively low proportion of lymphocytes (in particular B cells and cytotoxic T cells) and a complete absence of natural killer (NK) cells (Hilton *et al.*, 2019; Shebzukhov *et al.*, 2019).

Hepatic haemosiderosis and calcinosis cutis have been reported in naked mole-rats (Delaney *et al.*, 2013). *Post-mortem* examinations of captive individuals indicate a high prevalence of kidney-related pathologies such as renal tubular mineralization, and chronic progressive nephropathy (Delaney *et al.*, 2013), although there is no evidence that this has clinical relevance (T.B. Hildebrandt & S. Holtze, personal observations).

(5) Myth 24: naked mole-rats do not get tumours or cancer

Buffenstein *et al.* (2008) reported that no tumours had been found in more than 800 naked mole-rats in her colonies. Delaney *et al.* (2013) also reported no tumours in 138 necropsies of naked mole-rats that had died in zoos. However, Delaney *et al.* (2016) reported two cases of neoplasia, Taylor, Milone, & Rodriguez (2016) reported one presumptive and four spontaneous cases of neoplasia, and Cole *et al.* (2020) reported one further case. Naked mole-rats do appear to be cancer-resistant compared to similar-sized laboratory mice, which have cancer rates approaching 90% (Lipman *et al.*, 2004). However, no other mammals have such a high rate of spontaneous cancer as inbred strains of laboratory mice. Perhaps a better comparison would be with wild rodents or their (non-inbred) progeny in captivity, or with the guinea pig that is phylogenetically closer. Although cancer is widespread across the animal kingdom (Albuquerque *et al.*, 2018), to date, there are only relatively few data on cancer for most wild rodents. Whereas one study in wild-caught house mice found cancer rates of approximately 9% (Gardner *et al.*, 1973), another study reported that long-lived wild-derived mice die primarily of cancer (Harper, Leathers, & Austad, 2006).

Manskikh, Averina, & Nikiforova (2017) argue that the low cancer incidence recorded in naked mole-rats may be biased by high numbers of previously euthanized, presumably young, individuals examined by Delaney *et al.* (2013, 2016) as well as the relative scarcity of old individuals (Ruby *et al.*, 2018; Dammann *et al.*, 2019) in which cancer is more likely to manifest. Nevertheless, the reported tumour incidence is also close to zero in other bathyergids (Garcia Montero, Burda, & Begall, 2015; R. Šumbera, H. Burda, S. Begall & P. Dammann, unpublished data) as well as in long-lived beavers, porcupines (Ratcliffe, 1993), and chimpanzees (Varki & Varki, 2015). Thus, naked mole-rats do develop neoplasia, but appear to be cancer resistant, at least to the same extent as several other wild (rodent) species, exhibiting relatively high resistance to carcinogenesis considering their extraordinary lifespan.

(6) Myth 25: naked mole-rats have extremely large hyaluronan

Hyaluronan (HA) is a linear, anionic and acidic mucopolysaccharide composed of alternate N-acetyl-D-glucosamine and D-glucuronic acid units (Meyer & Palmer, 1934). Most HA molecules move freely in the extracellular matrix, while some bind to other macromolecules, including several hyaluronan-specific binding proteins and receptors. HA has numerous roles in physiological and pathological conditions although several of these roles have not been clinically confirmed (Laurent & Fraser, 1992; Bourguignon & Flamion, 2016; Bohaumilitzky *et al.*, 2017). HA is of interest because large HA [1–10 MDa, also called high molecular weight (HMW) HA], the most abundant form in almost all healthy tissues, has anti-angiogenic and anti-tumorigenic effects (Pandey *et al.*, 2013; Murai, 2015).

Tian *et al.* (2013) proposed that cancer resistance in naked mole-rats is mediated by a high content of ultra-HMW HA. Most naked mole-rat tissues were reported as staining strongly with Alcian blue, a marker of glycosaminoglycans, and electrophoresis of naked mole-rat tissue extracts on agarose gel revealed HA molecules with a molecular mass of 6–12 MDa, higher than in any animal tissue reported to date. Through binding to the CD44 receptor, the ultra-HMW HA was proposed to drive early contact inhibition, a potent anticancer mechanism that stops cellular proliferation at a low density, when cells come into contact with each other or with the extracellular matrix (Tian *et al.*, 2015; Takasugi *et al.*, 2020). This ultra-HMW HA could be produced by a highly expressed and mutated HA synthase (HAS2) gene displaying two serine substitutions at highly conserved sites (Tian *et al.*, 2013). Although the authors suggested this mutation could be an adaptation to the subterranean lifestyle, further sequence analyses across subterranean mammals revealed no obvious shared substitutions in that gene (Faulkes *et al.*, 2015). It is also unclear how a change in the active site of HAS2 could lead to longer HA molecules being extruded from the cell. Further reservations about this hypothesis derive from the fact that Alcian blue is known to bind to, and stain, predominantly sulfated glycosaminoglycans, without any specificity in binding to HA (Lin *et al.*, 1997). Furthermore, human cancer cells that overexpress naked mole-rat HAS2 produced HA of highly variable sizes depending on the type of host cell: HA of similar size to human HAS2-derived HA when expressed in pancreatic cancer cells (Huang, Zhao, & Radi, 2014) and HA of larger size when expressed in breast cancer cells. In pancreatic cells, the effect of naked mole-rat HAS2 was even tumour-promoting (Zhao *et al.*, 2019). Recently, Kulaberoglu *et al.* (2019), using atomic force microscopy, showed that HA extracted from naked mole-rat tissues had a very different structure, including coiling and gel-like behaviour, compared to HA extracted from human skin. They hypothesized that these properties would endow naked mole-rat skin with more elasticity. Hence, it is likely that HA and its metabolism in naked mole-rats are different from those of other rodents, but the claim of a huge (>6 MDa) HA preventing all naked mole-rat cells and tissues from neoplasia and metastasis is not convincing. Furthermore, Tian *et al.* (2013) claim that naked mole-rat cells with unaltered HA expression are resistant to oncogenic transformation using a combination of oncogenes which reliably transform mouse and rat fibroblasts [i.e. SV40 large T antigen and oncogenic Harvey rat sarcoma (HRAS)]. A recent study has failed to reproduce these findings and found naked mole-rat cells to be susceptible to oncogenic transformation, implying that their cancer resistance is mediated by a non-cell-autonomous mechanism (Hadi *et al.*, 2020).

(7) Myth 26: naked mole-rat cells have early contact inhibition that prevents cancer

Seluanov *et al.* (2009) reported that naked mole-rat fibroblasts in cell culture fail to reach confluency. Tian *et al.* (2015) argued that confluency could be obtained by adding hyaluronidase to the medium and that this is the mechanism by which they avoid cancer. Confluent fibroblast growth in cell culture, with and without the addition of hyaluronidase, has been observed by several authors (T. B. Hildebrandt, N. Kichler, S. Holtze & M. Vyssokikh, in preparation). By contrast, the viscous nature of the supernatant of naked mole-rat fibroblast cell cultures reported by Tian *et al.* (2013) has not been observed by any of these authors, despite comparable culture conditions.

(8) Myth 27: naked mole-rats are non-ageing

Longevity is well known to correlate with body size in non-flying mammals (Malgalhães, Costa, & Church, 2007). The maximum lifespan of the approximately mouse-sized naked mole-rat at 33 years (Ruby *et al.*, 2018) far exceeds that predicted on the basis of this correlation. A few other species, notably humans, are similarly strong upward outliers. Few laboratories or zoos have maintained naked mole-rat colonies for more than 35 years, so it is possible that this boundary will be extended further. Based on historical lifespan data from more than 3200 naked mole-rats collected over nearly 40 years, Ruby *et al.* (2018, p. 12) even concluded that naked mole-rats were 'non-ageing mammals' because the likelihood of mortality apparently did not increase with age in their analysis. Dammann *et al.* (2019) expressed doubts about this conclusion because the data set analysed by Ruby *et al.* (2018) was strongly skewed toward young cohorts (<8 years) in which demographic ageing is not expected to occur. Furthermore, fewer than 1% of the individuals included were observed for 18 years or longer, meaning that the age classes in which demographic ageing would be expected to occur were extremely under-represented.

The proposal that naked mole-rats do not show signs of ageing is undermined by much of the literature on the longest studied colonies. In one of the first reports of their unusual longevity, Buffenstein & Jarvis (2002, p. 7) note that 'older naked mole-rats are not as active as younger individuals. Older naked mole-rats can also be differentiated on sight from younger animals… Their skin is much lighter, thinner, and less elastic than that of younger individuals…; the skin of our oldest individual resembled parchment…'. Moreover, several typical mammalian age-related lesions of muscles, bone, heart, liver, and eye, including sarcopenia, osteoarthritis, a decline in articular cartilage thickness of the condyles, lipofuscin accumulation in several organs, eye cataracts, and kidney fibrosis have been described in naked mole-rats older than 26 years (Edrey *et al.*, 2011).

These results are consistent with observations in our colonies. Furthermore, like the mouse and human liver, naked mole-rat liver displays an age-related reduction of specific detoxification pathways (Heinze *et al.*, 2018). Thus there is ample evidence of a late onset of senescence in naked mole-rats, but this does not mean that they are 'non-ageing'.

VI. TAXONOMY

(1) Myth 28: naked mole-rats are the single member of a taxonomic family

The taxonomic status of *Heterocephalus* is not so much a myth as a scientific error. Phylogenetic analysis has shown that the genus *Heterocephalus* is sister group to the lineage leading to other bathyergids (reviewed in Faulkes & Bennett, 2013). Due to many morphological, genetic, social, and ecological differences, recently this genus has been raised to family level (Patterson & Upham, 2014). However, recognition of family rank from a lower taxonomic level (subfamily) is subjective, and the mole-rat research community does not generally follow this ranking for good reason. There are certainly differences between naked mole-rats and the other bathyergids (e.g. lack of fur). However, many diagnostic features described by Patterson & Upham (2014) are quantitative (e.g. length of tail, digit, and manus) while others (e.g. inbreeding and rare dispersal) are misunderstandings (see Sections IV.9 and IV.8). Some characteristics described as unique to naked mole-rats rats are present in other bathyergids, e.g. insensitivity to some algogens (Eigenbrod *et al.*, 2019) or cancer resistance (see Section V.5). One argument for elevating *Heterocephalus* to its own family was its ancient divergence from the last common ancestor of the other mole-rat species. This divergence was estimated at 31.2 Mya (Patterson & Upham, 2014), much earlier than the diversification of related families such as Petromuridae and Thryonomidae (estimated at 25 Mya by Huchon & Douzery, 2001). However, recent analyses suggest that *Heterocephalus* diverged only 23 Mya (Bryja *et al.*, 2018). In view of the combined weight of these various considerations, the co-authors of this review endorse the common practice of retaining *Heterocephalus* within the family Bathyergidae.

VII. CONCLUSIONS

(1) Naked mole-rats do have many unique adaptations that are likely to be extremely valuable for understanding senescence and developing new therapies. Skulachev *et al.* (2017) and Popov & Skulachev (2019) provide extensive lists of naked mole-rat adaptations, some of which have not been discussed herein. A more holistic view of their adaptations is likely to be more productive than focusing on only an individual characteristic of this very unusual species.

(2) In addition to a holistic view of naked mole-rats, we also suggest that researchers should consider the similarities and differences within the whole family Bathyergidae, or perhaps all subterranean rodents, particularly including the family Spalacidae (Fang *et al.*, 2014*a*; reviewed in Nevo, 1999). Many of these species share the unusual adaptations that have attracted so much attention in naked mole-rats. Understanding the broader phylogenetic context will be essential for understanding the evolution of these adaptations.

(3) Many of the persisting myths about naked mole-rats risk shaping the thinking of future biologists away from productive discoveries, wasting time and resources, and ultimately slowing scientific progress and delaying the discovery of new therapies. We hope that this review will help to avoid such wasted effort.

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