The Demographic and Evolutionary Consequences of Fertility Reduction in Rats: How Pesticides and Sterilants Act Like Sexual Selection

Stephen M. Shuster
Department of Biological Sciences, Northern Arizona University, Flagstaff, Arizona, and
Wisdom Good Works, Flagstaff, Arizona
Cheryl A. Dyer, **Morgan Boatman**, **Aliana Gonzalez-White**, **Sheila Mosher**, and **Loretta P. Mayer**
Wisdom Good Works, Flagstaff, Arizona

ABSTRACT: Rat population control is complicated by the rapid evolution of non-responsiveness to rodenticide treatment within populations. Population control using contraceptives could mitigate evolved resistance if non-responsiveness to contraceptives evolves more slowly than non-responsiveness to rodenticides. Our presentation has two parts. First, we use an age-dependent demographic model and classic data from natural populations to explore how contraceptives may control rat population size. We show that: (a) fertility reduction applied early in female lifetimes is effective in controlling rat population growth, and (b) is effective in controlling rat populations that are expanding. Consistent with model predictions, (c) field application of contraceptive bait decreased the total number of rats and the proportion of juvenile to adult rats observed in camera traps over a one-year urban study. Secondly, we illustrate a method for delaying and possibly eliminating the evolution of non-responsiveness to pest control treatments. We show that: (a) using simulations and estimates of the variance in relative fitness, the selection responsible for the evolution of non-responsiveness to pesticides and sterility-inducers resembles sexual selection, and therefore (b) can be orders of magnitude stronger than that for untreated populations. In contrast, (c) when contraceptives are used to reduce the fertility of a pest species, with non-responders embedded within such populations, the opportunity for selection favoring non-responsiveness is reduced to that occurring by chance alone. Our results indicate that contraceptives are more effective at controlling pest populations and slowing the evolution of non-responsiveness than treatments that cause sterilization or death in target species, findings with significant implications for the management of pest and pathogen species through fertility control.

KEY WORDS: contraceptives, evolved resistance, fertility control, pest management, rats, *Rattus* spp., rodent control, rodent life history

Proceedings, 31st Vertebrate Pest Conference (R. M. Timm and D. M. Woods, Eds.)
Paper No. 49. Published December 27, 2024. 8 pp.

INTRODUCTION

Rats are worldwide pests, associated with crop destruction and human disease (Leslie et al. 1952, Singleton and Petch 1994, Meerburg et al. 2009, Diaz et al. 2010, Buckle 2012, Pyzyna et al. 2014). Current methods for control involve mainly rodenticides and sterilants. As shown elsewhere (Boyle 1960, McNichol 1985, Rost et al. 2004, Pelz et al. 2005, Ishizuka et al. 2008), evolved resistance is the inevitable consequence of such treatments. Most researchers agree that evolved resistance of pest and disease organisms to human methods to control them, are among the most significant problems of modern times (Garrett 1994, Palumbi 2001, Davies and Davies 2010, Frieri et al. 2016, Gould et al. 2018).

Fertility control offers a possible solution to these problems. Most sources advocate sterilization for population control, although current methods are labor intensive (Tyndale-Biscoe 1994, Kirkpatrick 2007, Jacob et al. 2004, Massawe et al. 2018), environmentally challenging (Norbury 2000, Ruiz-Suárez et al. 2014) or empirically uncertain (Drury et al., 2017). Moreover, because these methods deliver their intended effects (i.e., death or sterility) to most individuals in their target populations (often over 90% of individuals), theoretical (Magiafoglou et al. 2003, Drury et al. 2017, Shuster et al. 2018) as well as field studies (Kirkpatrick 2007) suggest that such methods will likely favor the evolution of resistance to these treatments.

We argue that contraceptives provide a superior means for accomplishing most pest and disease control goals because they simultaneously reduce pest population size, and they reduce the selection that can favor resistance to treatment. Our three objectives are to: (1) show how contraceptives can control rat and other rodent population growth; (2) explain how pesticides, sterilants, and any treatment that targets one sex within a pest species, can act like sexual selection, causing the rapid evolution of resistance to treatment by allowing only a small fraction of resistant individuals to breed; (3) lastly, we describe how contraceptives can reduce the strength of selection favoring the evolution of resistance to treatment in pest and pathogen populations.

MODELING POPULATION GROWTH

Matrix and Life Table Models

Most models of population growth use projection matrices to generate their results (reviews in Caswell 2018). However, because these methods are often difficult to manipulate and interpret without specific understanding of matrix and vector components within each model, we use life tables to illustrate our points (Leslie et al. 1952, Ricklefs 2006). The latter framework generates results that are identical to matrix models and are more transparent to the

Table 1. Life table for a hypothetical iteroparous rodent with 100 females as the initial population size.
Female age class (=x); female survival=$l_{(x)}$; number of female survivors within each class=$s_{(x)}$, age-specific female fertility=$m_{(x)}$, number of female offspring=$o_{(x)}$; % of female census at t+1; finite rate of increase=λ; intrinsic rate of increase=r= ln(λ). (Modified from Shuster et al. 2023).

Age (x)	Census (t=0)	Survival $l_{(x)}$	Survivors $s_{(x)}$	Fertility $m_{(x)}$	Offspring $o_{(x)}$	Census (t+1)	%
0	20	0.5		0	0	74	0.66
1	10	0.8	10	1	10	10	0.09
2	40	0.5	8	3	24	8	0.07
3	30	0	20	2	40	20	0.18
4	0	0	0	0	0	0	0.00
Totals	**100**		**38**		**74**	**112**	**1**
						λ =	1.12
						r=	0.11

manipulations we will illustrate (see Shuster et al. 2023).

Life tables begin by identifying schedules of age classes and census data (Table 1). We identify five age classes (x = 0-4) with age-specific population census data, c(x) at time t=0 for 100 individuals. Next, we identify survival probabilities l(x), for each age class, where the distribution of surviving individuals at age s(x), equals the product [c(x-1) * l(x-1)]. Age-specific fertility is then identified, where m(x) indicates the number of offspring females in each life stage produce. Note that the sum of each of these values generates the expected lifetime reproductive output of each female, or the gross reproductive rate (GRR; Leslie et al. 1952). For each age class, we identified the distribution of offspring produced, where offspring number at age x, o(x), as the product [s(x) * m(x)].

To generate the population census at t=1, we projected the sum of all offspring, Σ o(0-4) in generation t=0 into c(0)=74 individuals at t=1, and projected the 38 survivors in age classes 1-3 over to the census column for t=1 (Table 1). The sum of these quantities equals 112, which indicates that the population has increased in size from its initial value at t=0 (=100 individuals). Notice too that the fraction of newly produced offspring at time t=1 is 66%, greater than any of the surviving age classes in this population. This indicates that the largest fraction of the population consists of newly born offspring, also as expected in growing populations.

The proportion of the total population in each age class, x, at time t=1, P(x)t=1, as c(x)t=1 / Σ c(x)t=1, and the net reproductive rate, λ = Ro, as the ratio of the sum of the population census at time t=1 divided by the sum of the population census at time t-1, or Σ c(x)t=1 / Σ c(x)t-1. The intrinsic rate of increase is calculated as ln(Ro) = r. Iteration of this process over several generations shows how the population will continue to grow if reproduction occurs at this rate (grey curve, Figure 1).

Age-specific Reproduction in Population Growth Models

We considered the effects of reproduction by different ages classes within a population by collapsing the total reproduction by females within the population into particular age classes (Shuster et al. 2023). To examine early reproduction, we collapsed all six of the expected lifetime progeny, or gross reproductive rate (GRR), produced by the average female into age class c(1). To examine reproduction in mid-life, we collapsed lifetime female reproduction into age class c(2). To examine reproduction late in female lifetimes we collapsed lifetime female reproduction into age class c(3). Compared to the Control curve for population growth described above, reproduction concentrated early in female lifetimes accelerates the rate of population growth, reproduction in the middle of female lifetimes overlaps the Control curve and reproduction late in female lifetimes stabilizes female population size near zero (Figure 1).

Combining Age-specific Reproduction with Reduced Fertility

Reducing total fertility stepwise by individual offspring such that the GRR ranges from six to two offspring allows visualization of the combined and relative effects of age specific reproduction and fertility reduction. Note that compared to the Control curve for population growth generated in Figure 1, reproduction concentrated early in female

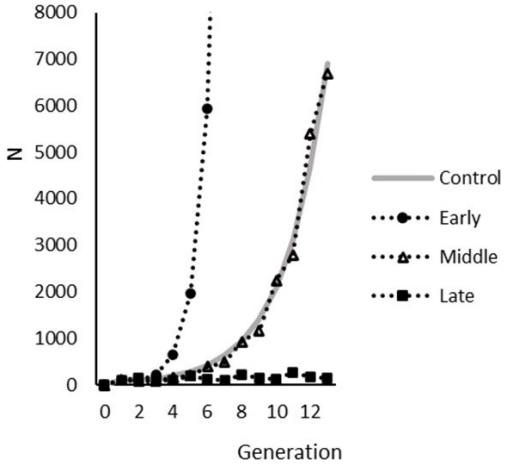

Figure 1. The effect of age-specific fertility on the growth of a hypothetical iteroparous rodent population; Control (grey curve) represents population growth over 12 generations resulting from parameters defined in Table 1; age-specific reproduction was accomplished by collapsing lifetime fertility (GRR = 6 offspring) into Early, Middle and Late age classes; Early reproduction accelerates the rate of population growth, reproduction in the Middle of female lifetimes overlaps the Control curve and reproduction late in female lifetimes stabilizes female population size near zero. (Modified from Shuster et al. 2023).

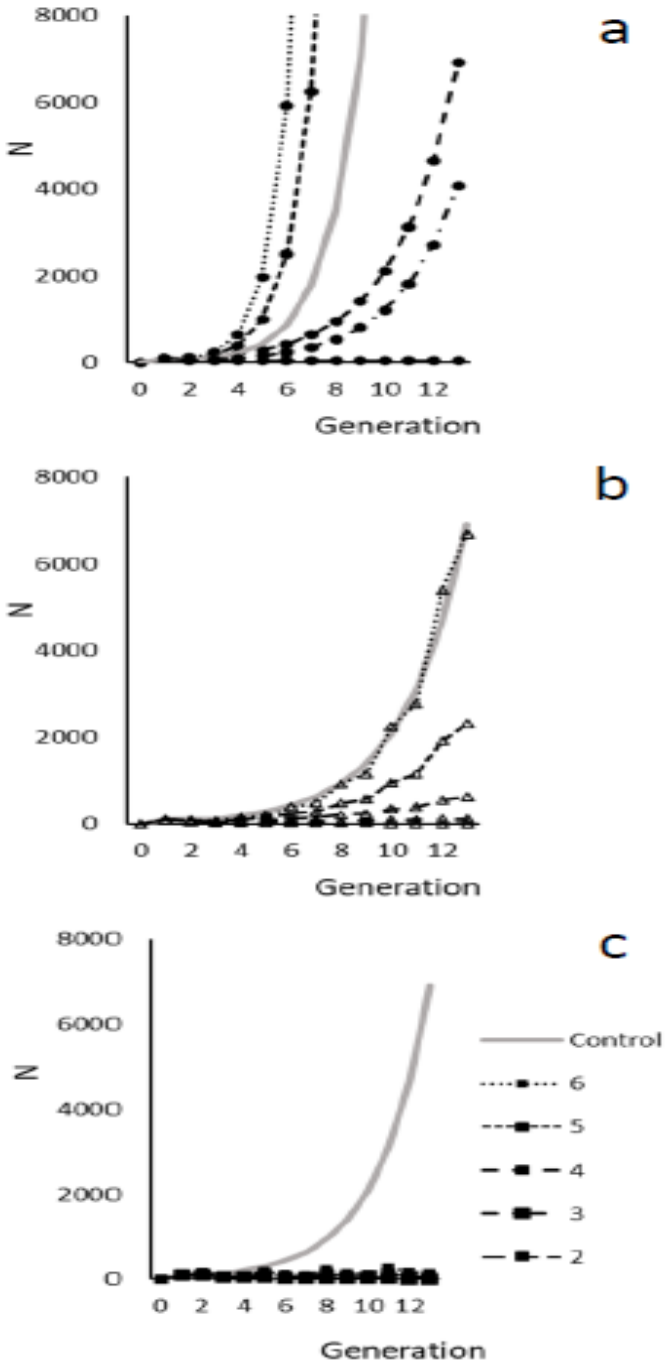

Figure 2. The effect of age-specific reproduction and reduced fertility on a hypothetical iteroparous rodent population; Control (grey curve) represents population growth over 12 generations resulting from parameters defined in Table 1; age-specific reproduction was accomplished by collapsing lifetime fertility (GRR = 6 offspring) into Early, Middle and Late age classes; fertility reduction was accomplished by reducing total fertility stepwise by individual offspring such that the GRR decreased from six to two offspring; reduction in female fertility was focused at (a) Early, (b) Middle and (c) Late ages; reproduction concentrated Late in female lifetimes combined with fertility reduction (c) showed the greatest tendency to suppress population growth. (Modified from Shuster et al. 2023).

lifetimes, combined with fertility reduction, generates a family of curves surrounding the Control curve, with only severe reduction in fertility (GRR = 2) effectively suppressing population growth (Figure 2a). Reproduction concentrated in the middle of female lifetimes, combined with fertility reduction, also generates a family of curves but these are concentrated to the right of the Control curve; i.e., fertility reduction is more effective in restricting population growth but only GRR <4 suppresses it (Figure 2b). Reproduction concentrated late in female lifetimes combined with fertility reduction shows that no fertility reduction is necessary to suppress population growth (Figure 2c).

Populations that are expanding are widely thought to be resistant to efforts to control their growth (Shi et al. 2002). Reproduction concentrated into early, middle life stages, combined with stepwise fertility reduction, allowed population growth nearly unabated except when extreme fertility reduction was applied (Figure 3a; GRR = 2). In the case of early reproduction, the population leveled off at 9×10^4 by generation 14 (Figure 3a) and decreased by generation 14 within middle life with such fertility reduction (Figure 3b). However, with reproduction Late in life, GRR = 5 caused the population to oscillate between 5.5 and 7.5×10^4 individuals and GRR <5 caused populations to decrease, and with GRR = 2 to crash by generation 24 (Figure 3c).

These simulations illustrate that with the above population parameters, population growth in a hypothetical, iteroparous rodent population can be controlled by: (1) delaying the age of first reproduction and (2) reducing fertility. In general, fertility control methods that suppress early reproduction and reduce fertility appear to be most effective, even reversing growth in populations that are expanding.

Application to Field Populations of Rats

Leslie et al. (1952) studied the fertility of brown rats, *Rattus norvegicus*, in English corn ricks for three seasons (1939-1941). They combined information from this population with data from laboratory populations to generate a stable age distribution for 10,000 female rats in nature. To test the generality of our framework, we inserted these data into a life table, increasing the number of age classes to 10 and adjusting the census data downward to 1,000 females (Table 2), As expected based on Leslie et al. (1952), these data generated an expanding hypothetical population that exceeded 2×10^6 individuals by generation 9 (Shuster et al. 2023, Figure 4).

We next imposed fertility reduction ranging from 10-30% (3-9 offspring) focused early [ages 1 (90–149 days), 2 (150–209 days), 3 (210–269 days)], in the middle [ages 4 (270–329 days), 5 (330–389 days), 6 (390–449 days)], and late [ages 7 (450–509 days), 8 (510–569 days), 9 (570–630 days)] within female lifetimes (see Methods in Shuster et al. 2023). While fertility reduction focused in the middle and late in female lifetimes had no recognizable effect on population growth, 10% reduction slowed population growth and 20-30% reduction caused population sizes to decrease (Shuster et al. 2023, Figure 4a-c). To explore how this framework might respond to fertility control imposed after this hypothetical population had expanded for 12 generations, we imposed fertility control as described above

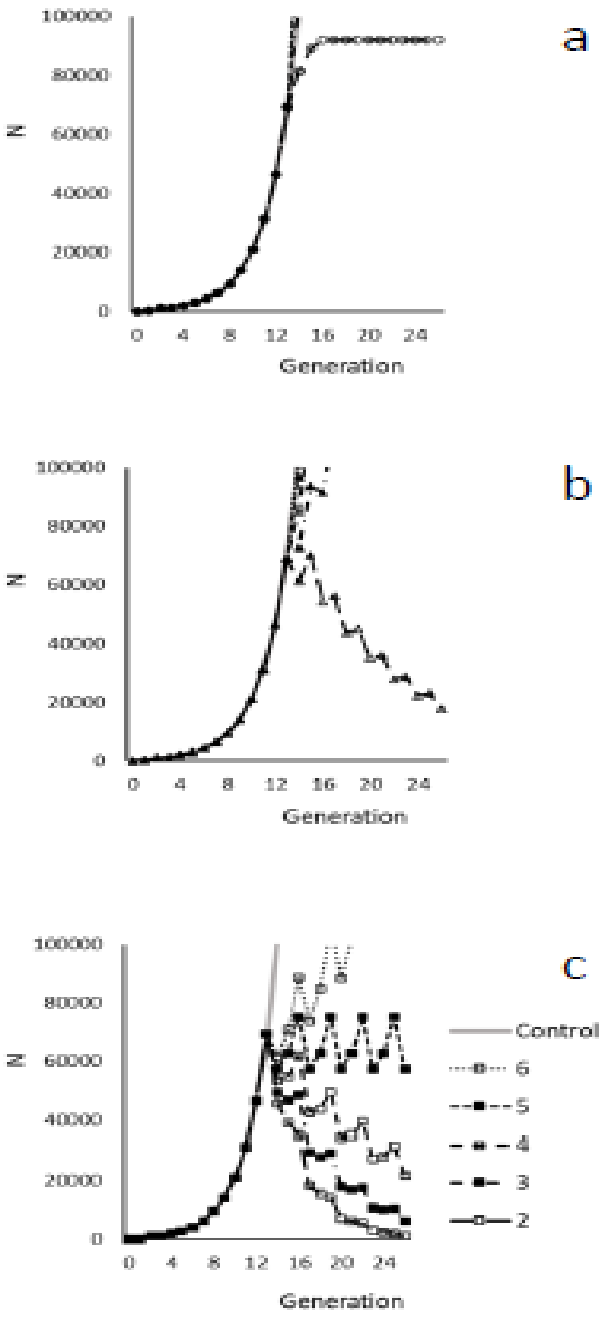

Figure 3. The effect of age-specific reproduction and reduced fertility on a hypothetical iteroparous rodent population that has been allowed to expand for 12 generations; Control (grey curve) represents unchecked population growth resulting from parameters defined in Table 1; age-specific reproduction was accomplished by collapsing lifetime fertility (GRR = 6 offspring) into Early, Middle and Late age classes; fertility reduction was accomplished by reducing total fertility stepwise by individual offspring such that the GRR decreased from six to two offspring; even for an expanding population, reproduction concentrated in female lifetimes combined with fertility reduction (c) showed the greatest tendency to suppress population growth. (Modified from Shuster et al. 2023).

when the hypothetical population had exceeded 1.8×10^8 (Shuster et al. 2023, Figure 5).

Again, while fertility reduction imposed in the middle and late in female lifetimes had no recognizable effect on population growth, fertility reduction ranging only from 20-30% imposed early in female lifetimes caused this expanding population to decrease in size and crash by generation 24 with fertility reduction of 40% (Shuster et al. 2023, Figure 5a-b). Collectively, these results suggest that life history parameters, including actual data on rat life histories (Leslie et al. 1952) and specifically imposing fertility reduction early in female lifetimes, can be manipulated to control rat populations that are expanding.

FERTILITY CONTROL

Fertility Control in the Laboratory

Fertility control of rats has been abundantly demonstrated under laboratory conditions (Mayer et al. 2002, Mayer et al. 2004, Dyer and Mayer 2014, Dyer et al. 2013, Siers et al. 2017). Witmer et al. (2017) showed that treatment with the contraceptive, Contrapest (CP), a proprietary combination of 4-vinylcyclohexene diepoxide and triptolide, is effective within two weeks, has persistent effects over four months, and is reversible within six months. The results of this experiment were clear cut (Figure 4). Only Control (Ctrl) pairs were fertile in Breeding Round 1 (BR1) indicating that CP treatment was effective within 15 days. Only Ctrl pairs were fertile in BR2, and in BR3, while Ctrl pairs were fully fertile the fertility of Treatment (Tmt) pairs was reduced by over 90%, indicating that the effects of CP treatment persisted for over four months. Fertility had returned to both Tmt and Ctrl pairs in BR4, and while somewhat reduced, the fertility of both groups was not significantly different, either from one another or from the fertility of Ctrl pairs in BR1-3, indicating that the effects of CP on the fertility of male and female rats was reversible within six months (Figure 4). These results answer four central questions in fertility control applications:

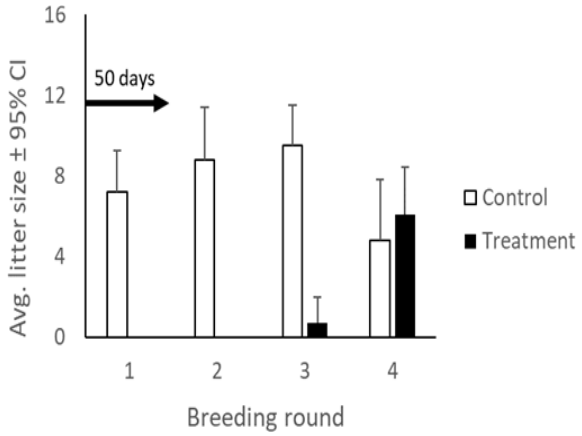

Figure 4. Summary of results from Witmer et al. (2017), showing the contraceptive effects of Contrapest, a proprietary combination of 4-vinylcyclohexene diepoxide and triptolide, on male and female *Rattus norvegicus*, wild-caught near Fort Collins, CO; treatment is effective within two weeks, has persistent effects over four months, and is reversible within six months; see text for experimental details.

Table 2. Life table for brown rats (*Rattus norvegicus*); the initial population size includes 1,000 females.

The census of females at each age(x), is shown in 60-day intervals (except for age 0); female age class (=x); female survival=$l_{(x)}$; number of female survivors in each class=$s_{(x)}$, age-specific female fertility=$m_{(x)}$, number of female offspring=$o_{(x)}$; % of female census at t+1; finite rate of increase=λ,; intrinsic rate of increase=r= ln(λ). (Modified from Shuster et al. 2023.)

Age (x)	Days	Census (t=0)	Survival $l_{(x)}$	Survivors $s_{(x)}$	Fertility $m_{(x)}$	Offspring $o_{(x)}$	Census (t+1)	%
0	0-	751.4	0.751		0.00	0	2178	0.77
1	90-	147.0	0.196	565	3.18	1795	565	0.20
2	150-	60.2	0.410	29	5.47	157	29	0.01
3	210-	24.7	0.410	25	5.87	145	25	0.01
4	270-	10.1	0.409	10	5.40	55	10	0.00
5	330-	4.1	0.406	4	4.61	19	4	0.00
6	390-	1.6	0.390	2	3.28	5	2	0.00
7	450-	0.6	0.375	1	2.13	1	1	0.00
8	510-	0.2	0.333	0	1.04	0	0	0.00
9	570-	0.1	0.500	0	0.22	0	0	0.00
10	630-	0.0	0.000	0	0.00	0	0	0.00
Totals		**1000**		**635**	**31.20**	**2178**	**2813**	**1.00**
							λ =	2.81
							r =	1.03

(1) how soon is treatment effective? (2) how long does treatment last? (3) is treatment reversible? (4) how soon does treatment reversal occur?

Fertility Control in the Field – Washington DC, 2019-2020.

In field trials, Contrapest (CP) also proved effective in reducing the population size of brown rats (*R. norvegicus*) inhabiting two urban alleys (Oglethorpe Street; Reservoir Road) in a 12-month application in Washington, D.C. in 2019-2020 (Shuster et al. 2023). Before and during this deployment, second generation anticoagulant rodenticides (SGARs) had been used by residents and businesses to control rats. Digital cameras showed high densities of rats were present at both locations at the beginning of the study (Figure 5), as expected if the efficacy of treatment with SGARs had decreased over time. Liquid CP bait stations at camera sites replenished monthly showed increasing consumption until pandemic-associated changes in service personnel prevented a more complete record. Nevertheless, the total number of rat images recorded on cameras decreased significantly over the 12-month study, and importantly, the proportions of juvenile rats in both locations also decreased significantly (Shuster et al. 2023). These results combined with those above suggest that in theory, in the laboratory, and over the duration of the above field application, fertility control is effective in decreasing the population size of brown rats.

EVOLVED RESISTANCE TO PESTICIDES, STERILANTS AND CONTRACEPTIVES

How Rodenticides and Sterilants Act Like Sexual Selection

Sexual selection occurs when individuals of one sex produce offspring at the expense of individuals of the same sex (Shuster and Wade 2003), or as stated originally by Darwin (1871), "…if each male secures two or more females, many males cannot pair." Genetic monogamy in a hypothetical population consisting of 100 males and 100 females, and in which each male and each female in the population pairs for life with a single other individual, illustrates circumstances in which sexual selection does *not* exist (Figure 6; Shuster and Wade 2003). In contrast, random mating and greater mating skew shows how some individuals might mate more than once, here with as many as four females. However, the result of such success by these males, as Darwin observed, is that 36% of other males in this population are excluded from mating. In the most extreme case, if only a single male mates within this population, 99% of males are excluded entirely from reproduction.

This example also illustrates how, like sexual selection, the most effective rodenticides allow the fewest breeders to remain in treated populations. Because these favored individuals are unaffected, or at least are unresponsive to rodenticide treatment, these resistant individuals transmit their resistance to offspring. Because susceptible rodent competitors are eliminated from the local habitat, it is not surprising that resistance to rodenticides, as well as other lethal treatments, can so rapidly, so consistently, and so pervasively evolve throughout the world (Pelz et al. 2005, Endenpols et al. 2013). The question is, how can the process responsible for evolved resistance to rodenticides, akin to one of the strongest evolutionary forces known, be mitigated?

The Opportunity for Selection

We can understand how evolved resistance to rodenticides can be controlled by first understanding how the strength of selection can be measured in natural populations (Crow 1958, Crow 1962, Wade 1979, Shuster and Wade 2003). In any population, the variance in fitness, measured in offspring numbers among individuals, V_O, is proportional to the strength of selection. Crow (1958) showed that when the variance in fitness is divided by the squared average in fitness, O^2, it equals the variance in *relative* fitness, $I = V_O/O^2 = V_{\tilde{o}}$, or what Crow described as, *the opportunity for selection*. This parameter allows inferences about *how* selection acts on traits, and in this context, how strongly selection may act to favor non-responsiveness.

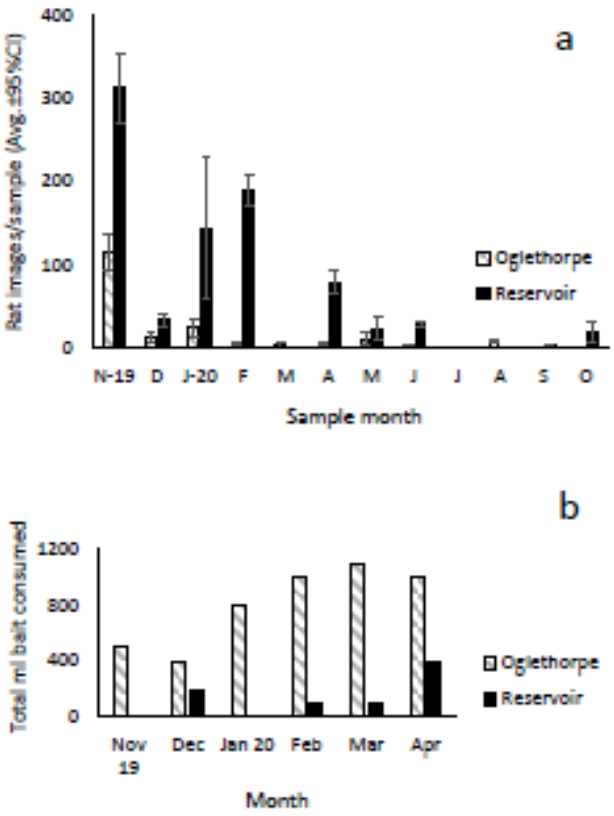

Figure 5. Effect of Contrapest in reducing the population size of brown rats (*R. norvegicus*) inhabiting two urban alleys (Oglethorpe Street; Reservoir Road) in a 12-month application in Washington, DC between November 2019 and October 2020; (a) total rat images recorded in camera samples decreased in both locations significantly over the 12-month study; (b) consumption of contraceptive bait appeared to increase in both location over the first six months of the study; hatched bars = Oglethorpe; black bars = Reservoir, error bars = 95%CI. (Modified from Shuster et al. 2023).

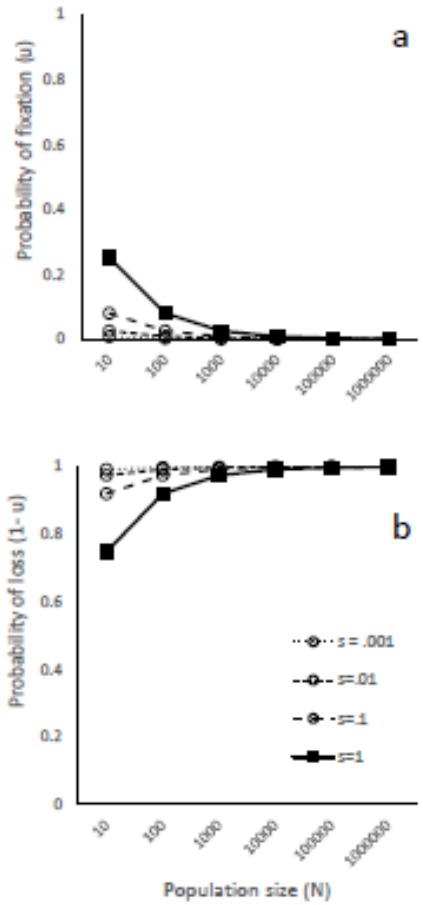

Figure 6. The effects of selection and drift on advantageous alleles; (a) selection on an advantageous allele is weak when N is large but even when populations are comparatively small (N=100) the probability of fixation of a favorable allele is low (<0.08); (b) the probability of loss of an advantageous allele via genetic drift is large when N is large but even when populations are comparatively small (N=100) the probability of loss is high (>0.92); contraceptives embed non-responders within a genetically variable population.; they reduce selection on resistance AND they allow loss of resistance alleles by drift.

The Opportunity for Selection on Non-responsiveness

Total female rat fertility, in theory and in nature depends on the mean and variance in the number and the size of litters that individual female rats produce within their lifetimes (Leslie et al. 1952). Contraceptives work by reducing the magnitude of one or both of these life history parameters (Shuster et al. 2018), and as shown above, can reduce female gross reproductive rates (GRR) and thereby cause rat population size to decline (Shuster et al. 2023). Rodenticides also reduce population size, but they do so by imposing lethal truncation selection, whereby only nonresponsive individuals survive and all others, i.e., all responsive individuals, with their death, are eliminated from the population altogether. Note that sterilants, including CRISPR-Cas9 procedures or gene drives that induce male sterility (Drury et al. 2017) work in the same way. While sterile individuals may persist within the population and influence ecological processes, only non-responsive individuals will contribute to future generations with evolved resistance the inevitable result.

Modeling Rat Life History in the Context of Fertility Control

To explore whether and why this might be so, Shuster et al. (2018) calculated the opportunity for selection on untreated rat populations, populations exposed to rodenticides, populations exposed to contraceptives, and on the latter two populations in which alleles associated with resistance to these treatments were presumed to exist (see Shuster et al. 2018, Fig. 4a).

The opportunity for selection for simulated, untreated populations with maximum fertility (litter size=litter number=15) equaled that expected by chance alone, or $I_{females} = 0.06$ (Shuster et al. 2018, Figure 4b). Fertility reduction imposed on these populations so that litter size = litter number = 5) increased the opportunity for selection by nearly 4-fold ($I_{females} = 0.23$), although the total opportunity

for selection remained relatively weak and was no different from values expected when selection acts by chance (Shuster et al. 2018).

In contrast, the opportunity for selection estimated for simulated population exposed to rodenticides, in which 90-99% of the population was removed, regardless of total female fertility estimated as described above, the opportunity for selection on females increased to more than $I_{females} = 1.0 \times 10^4$, over 1.65×10^5 fold (Shuster et al. 2018, Figure 5). Alleles conferring resistance to rodenticides within these populations would presumably experience positive selection of this magnitude as well, consistent with the observed rapid evolution of resistance to rodenticides now recorded in many treated rodent populations (Song et al. 2011, Buckle 2012, Endepols et al. 2013).

Shuster et al. (2018, Fig. 5) explored the effect of embedding individuals with maximum fertility (J=K=15) within populations whose fertilities were reduced by contraceptives and found the opportunity for selection in these simulated populations was reduced to values indistinguishable from those of untreated populations. In contrast, females bearing alleles conferring resistance to rodenticides, would be the only females that survived rodenticide treatment. Because all responsive females in such populations would be removed, selection favoring resistance to rodenticides would be enormously strong, as our simulations confirmed.

The Importance of Selection and Drift

These results are supported by classic population genetic theory. Haldane (1927) and later Wright (1942) argued that selection on advantageous alleles, in this case such as those associated with non-responsiveness to rodenticides or contraceptives in treated population, would be extremely weak when population size is large. The probability that such alleles would become fixed would equal $u = (2s/\pi N)^{1/2}$, where s equaled the selection coefficient (Wright 1942). Yet simulations using these equations show that even when population size decreases by orders of magnitude, the probability of allele fixation remains small (Figure 6a).

Kimura (1962) reached a related conclusion by suggesting that rare, advantageous alleles were almost certain to be lost from large populations by genetic drift, showing that the probability of loss of an advantageous allele would equal 1-u or $1.128(s/2N)^{1/2}$, a value that remains remarkably high when population sizes are small (Figure 6b). Both sets of simulations reveal the advantages of procedures likely to preserve genetic diversity within treated populations, such as fertility control, compared to those, such as rodenticides, sterilants and other similar treatments, which radically reduce genetic variation by truncation selection.

CONCLUSIONS AND FUTURE DIRECTIONS

Rats are indeed worldwide pests. However, our results suggest that control of rat and other rodent populations is possible using contraceptives and is more likely to be successful than rodenticides and sterilants. Our simulations indicate that whereas these latter treatments can impose on pest populations the strongest selection that is now known, orders of magnitude stronger even than sexual selection, contraceptives appear capable of reducing population size as well as mitigating the selection that could lead to the evolution of resistance to contraceptive treatment. Our results are generalizable to other pest and pathogen control strategies which now focus on extirpation of target species. We assert that lethal and sterilization approaches will inevitably lead to the evolution of resistance to treatment. If contraceptives can control population size as well as mitigate evolved resistance to treatment, a new era of pest and pathogen control may be at hand.

ACKNOWLEDGMENTS

We are grateful to Open Philanthropy for their generous support of WGW.

LITERATURE CITED

Boyle, C. M. 1960. Case of apparent resistance of *Rattus norvegicus* Berkenhout to anticoagulant poisons. Nature 188(4749): 517-517.

Buckle, A. 2012. Anticoagulant resistance in the United Kingdom and a new guideline for the management of resistant infestations of Norway rats (*Rattus norvegicus* Berk.). Pest Management Science 69:334-341.

Caswell, H. 2018. Matrix population models: construction, analysis, and interpretation. Second edition. Sinauer Associates, Sunderland, MA.

Crow, J. F. 1958. Some possibilities for measuring selection intensities in man. Human Biology 30:1-13.

Crow, J. F. 1962. Population genetics: selection. Pages 53-75 in W. J. Burdette, editor. Methodology in human genetics. Holden-Day, San Francisco, CA.

Darwin, C. R. 1871. The descent of man and selection in relation to sex. Appleton, NY.

Davies, J., and D. Davies 2010. Origins and evolution of antibiotic resistance. Microbiology and Molecular Biology Review 9:417-433.

Diaz, J. C., Y. Song, A. Moore, J. N. Borchert., and M. H. Kohn. 2010. Analysis of vkorc1 polymorphisms in Norway rats using the roof rat as outgroup. BMC Genetics 11:43.

Drury, D. W., A. L. Dapper, D. J. Siniard, G. E. Zentner, and M. J. Wade. 2017. CRISPR/Cas9 gene drives in genetically variable and nonrandomly mating wild populations. Science Advances 3:e1601910.

Dyer, C. A., and L. P. Mayer. 2014. Sprague-Dawley female rat consumption of a liquid bait containing vinylcyclohexene diepoxide and triptolide leads to subfertility. Proceedings of Vertebrate Pest Conference 36:386-390.

Dyer, C. A., S. Raymond-Whish, S. Schmuki, T. Fisher, B. Pyzyna, A. Bennett, and L. P. Mayer. 2013. Accelerated follicle depletion in vitro and in vivo in Sprague-Dawley rats using the combination of 4-vinylcyclohexene diepoxide and triptolide. Journal of Zoo Wildlife Medicine 44(4s):S9-S17.

Endepols, S., N. Klemann, Y. Song, and M. H. Kohn. 2013. *Vkorc1* variation in house mice during warfarin and difenacoum field trials. Pest Management Science 69:409-413.

Frieri, M., K. Kumar, and A. Boutin. 2016. Antibiotic resistance. Journal of Infectious Public Health 10(4):369-378.

Garrett L. 1994. The coming plague: newly emerging diseases in a world out of balance. Farrar, Straus, and Giroux, New York, NY.

Gould, F., Z. S. Brown, and J. Kuzma. 2018. Wicked evolution: can we address the sociobiological dilemma of pesticide resistance? Science 360:728-732.

Haldane, J. B. S. 1927. A mathematical theory of natural and artificial selection. Part V: selection and mutation. Proceedings of the Cambridge Philosophical Society 23:838-844.

Ishizuka, M., K. D. Tanikawa, K. D. Tanaka, M. Heewon, F. Okajima, S. Q. Sakamoto, and S. Fujita. 2008. Pesticide resistance in wild mammals: mechanisms of anticoagulant resistance in wild rodents. Journal of Toxocology Science 33: 283-291.

Jacob, J., N. A. Herawati, S. A. Davis, and G.R. Singleton. 2004. The impact of sterilized females on enclosed populations of ricefield rats. Journal of Wildlife Management 68:1130-1137.

Kimura, M. 1962. On the probability of fixation of mutant genes in a population. Genetics 147:713-719.

Kirkpatrick, J. F. 2007. Measuring the effects of wildlife contraception: the argument for comparing apples with oranges. Reproduction Fertility and Development 19:548-552.

Leslie, P. H., U. M. Venables, and L. S. V. Venables. 1952. The fertility and population structure of the Brown Rat (*Rattus norvegicus*) in corn-ricks and some other habitats. Proceedings of the Zoologial Society of London 122:187-238.

Magiafoglou, A., M. Schiffer, A. A. Hoffmann, and S. W. McKechnie. 2003. Immunocontraception for population control: will resistance evolve? Immunology and Cellular Biology 81:152-159.

Massawe, A. W., R. H. Makundi, Z. Zhang, G. Mhamphi, M. Liu, H. J. Li, and S. R. Belmain. 2018. Effect of synthetic hormones on reproduction in *Mastomys natalensis*. Journal of Pest Science 91:157-168.

Mayer, L. P., P. J. Devine, C. A. Dyer, and P. B. Hoyer. 2004. The follicle-depleted mouse ovary produces androgen. Biology of Reproduction 71(1):130-138.

Mayer, L. P., N. A. Pearsall, P. J. Christian, C. M. Payne, M. K. McCuskey, S. L. Marion, I. G. Sipes, and P. B. Hoyer. 2002. Long term effects of ovarian follicular depletion in rats by 4-vinylcyclohexene diepoxide. Reproductive Toxicology 16(6): 775-781.

McNichol, A. D. 1985. A comparison of warfarin resistance and liver microsomal vitamin K epoxide reductase activity in rats. Biochimica Biophysica Acta 840:13-20.

Meerburg, G. M., G. R. Singleton, and A. Kijlstra. 2009. Rodent-borne diseases and their risks for public health. Critical Reviews in Microbiology 35:221-270.

Norbury, G. 2000. The potential for biological control of stoats (*Mustela erminea*). New Zealand Journal of Zoology 27(3): 145-163.

Palumbi, S. R. 2001. Humans as the world's greatest evolutionary force. Science 293:1786-1790.

Pelz, H.-J., S. Rost, M. Hünerberg, A. Fregin, A.-C. Heiberg, K. Baert, A. D. MacNicoll, C. V. Prescott, A.-S. Walker, J. Oldenburg, and C. R. Müller. 2005. The genetic basis of resistance of anticoagulants in rodents. Genetics 170:1839-1847.

Pyzyna, B. L., C. Cunningham, E. Calloway, C. Dyer, and L. Mayer. 2014. Liquid fertility management bait uptake by urban rats within New York City subway refuse rooms. Proceedings of Vertebrate Pest Conference 26:375-379.

Ricklefs, R. E. 2006. The economy of nature. Fifth edition. W. H. Freeman and Company, New York, NY.

Rost, S., A. Fregin, V. Ivaskevicius, E. Conzelmann, C. Hörtnagel, H.-J. Pelz, K. Lappegard, E. Seifried, I. Scharrer, E. G. D. Tuddenham, C. R. Müller, T. M. Strom, and J. Oldenburg. 2004. Mutations in *vkorc1* cause warfarin resistance and multiple coagulation factor deficiency type 2. Nature 427: 537-541.

Ruiz-Suárez, N., L. A. Henríquez-Hernández, P. F. Valerón, L. D. Boada, M. Zumbado, M. Camacho, M. Almeida-González, and O. P. Luzardo. 2014. Assessment of anticoagulant rodenticide exposure in six raptor species from the Canary Islands (Spain). Science of the Total Environment 485-486:371-376.

Shi, D., X. Wan, S. A. Davis, R. P. Pech, and Z. Zhang. 2002. Simulation of lethal control and fertility control in a demographic model for Brandt's vole, *Microtus brandti*. Journal of Applied Ecology 39:337-348.

Shuster, S. M., C. A. Dyer, B. Pyzyna, and L. R. Mayer. 2023. The demographic consequences of fertility reduction in rats and voles. Journal of Pest Science https://doi.org/10.1007 /s10340-023-01607-7

Shuster, S. M., B. Pyzyna, C. A. Dyer, and L. P. Mayer. 2018. The opportunity for sexual selection and the evolution of non-responsiveness to pesticides, sterility inducers and contraceptives. Heliyon 4 doi: 10.1016/j.heliyon.2018.e00943.

Shuster, S. M., and M. J. Wade. 2003. Mating systems and strategies. Princeton University Press, Princeton, NJ.

Siers, S. R., B. R. Pyzyna, L. Mayer, C. Dyer, I. L. Leinbach, R. T. Sugihara, and G. W. Witmer. 2017. Laboratory evaluation of the effectiveness of the fertility control bait ContraPest® on wild-captured black rats (*Rattus rattus*). Unpublished Report QA-2570. USDA APHIS WS, National Wildlife Research Center, Hilo, HI.

Singleton, G. R., and D. A. Petch. 1994. A review of the biology and management of rodent pests in Southeast Asia. Australian Center of International Agricultural Research 1-66.

Song, Y., S. Endepols, N. Klemann, D. Richter, F.-R. Matuschka, C.-H. Shi, M. W. Nachman, and M. H. Kohn. 2011. Adaptive introgression of anticoagulant rodent poison resistance between old world mice. Current Biology 21(15):1296-1301.

Tyndale-Biscoe, C. H. 1994. Virus-vectored immunocontraception of feral mammals. Reproduction Fertility and Development 6:281-287.

Wade, M. J. 1979. Sexual selection and variance in reproductive success. American Naturalist 114:742-764.

Witmer, G. W., S. Raymand-Whish, R. S. Moulton, B. R. Pyzyna, E. M Calloway, C. A. Dyer, L. P. Mayer, and P. B Hoyer. 2017. Compromised fertility in free feeding of wild-caught Norway rats (*Rattus norvegicus*) with a liquid bait containing 4-vinylcyclohexene diepoxide and triptolide. Journal of Zoo and Wildlife Medicine 48:80-90

Wright, S. 1942. Statistical genetics and evolution. Bulletin of the American Mathematical Society 48:223-246.