RESISTANCE TO ANTICOAGULANT RODENTICIDES: THE PROBLEM AND ITS MANAGEMENT

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Abstract

Rodent control was revolutionised by the introduction of anticoagulant rodenticides such as warfarin in the late 1940s and 1950s. Inherited resistance to warfarin was first detected in the United Kingdom in 1958, within a decade of its introduction. Since then, warfarin resistance has been found in a number of rodent species in many countries. Warfarin resistance in the brown rat is monogenic and associated with some deleterious effects. Cross-resistance to the modern anticoagulant difenacoum is now established in the United Kingdom. We review previous attempts to manage resistance and then consider some more speculative approaches based on principles of population biology. A major problem in resistance management is the difficulty of adequate resistance monitoring.

Introduction

Chemical control of rodents, especially in the region of food stores, differs qualitatively in a number of ways from control of other pests such as insects. Because rodent pests are physiologically very similar to the animals for which the stored food is destined (man, domesticated ungulates or poultry), selective toxicity to rodents is hardly ever possible. Hence the crude application techniques used to control insect pests (e.g. space spraying, admixture of powders with grain) are out of the question, and rodenticides must be applied sparingly and selectively in order to avoid contamination of the stored product, or other ways of accidentally poisoning non-target animals. Where possible poisons should be avoided altogether, and they sometimes can be avoided if a food store is rodent proofed by physical means and accidental spillages of food in and around the store are quickly cleared up (FAO, 1983). Also, fumigation with a non-residual compound such as phosphine will kill rodents as well as insects if carried out properly. However, rodents are often very mobile and may live in one place and feed elsewhere such that fumigation is only temporarily effective, and food stores are rarely designed and built

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with keeping out rodents as a main objective.

Trapping is another method of control that can sometimes be of value, but traps require a considerable amount of attention and are not adequate for achieving control of a bad infestation. Hence use of rodenticidal compounds is commonly necessary, and both their choice and application must take account of the risks of applying mammalian poisons in close proximity to foodstuffs.

In general, rodenticides are applied as poison baits. Baiting allows the amount of poison consumed in a treatment to be monitored and it is much easier to remove unused bait at the end of a treatment than, for example, a contact poison dust formulation (Marsh, 1983) which is picked up on the fur of an animal and ingested during grooming. The problem with poison baits is that the main commensal pests (the brown rat Rattus norvegicus Berk., the roof rat Rattus rattus and the house mouse Mus musculus) are notoriously wary of new objects such as bait trays, and of new foods. If a rodent eats a small quantity of bait and takes in a dose which is not lethal but makes the animal ill, it may avoid that bait possibly for the rest of its natural life (Meehan, 1984). Thus acute poisons such as zinc phosphide and scilliroside are ideally used following a period of pre-baiting with unpoisoned bait in order that rodents will have overcome their initial neophobia and may ingest a lethal dose before the onset of unpleasant symptoms (luckily, rodents lack the anatomical structure necessary for vomiting). Unfortunately, fast-acting, acute poisons which kill after a single dose are also dangerous to non-target vertebrates since the onset of symptoms is rapidly followed by death and there is no specific antidote. Also, such poisons require a high degree of operator skill for successful application, and are reckoned rarely to achieve a high level of kill (see Meehan (1984) for review).

The category of poisons that revolutionised rodent control is that of anticoagulants, about a dozen of which are in common use. The best known is warfarin, developed in the USA and first used as a rodenticide in the late 1940s. All anticoagulants work by blocking the vitamin K_1 oxidation-reduction cycle in the mammalian liver; oxidation of vitamin K_1 is essential for the production of clotting factors (Fig. 1). If the cycle is blocked, normal clotting of blood at sites of haemorrhage (external or internal) is prevented, blood is constantly lost and blood pressure falls, eventually leading to death. Warfarin is thought to have a higher affinity for vitamin K_1 epoxide reductase than does the epoxide, causing the build-up of the oxidised form of vitamin K_1 and cessation of the cycle (Fig. 1). Thus there is an effective antidote to anticoagulant poisoning; administration of vitamin K_1 drives the oxidation part of the cycle (allowing production of clotting factors again) until anticoagulant levels have dropped sufficiently to allow normal activity of vitamin K_1 epoxide reductase to be restored. Since the symptoms of anticoagulant poisoning do not appear for a few days after ingestion of the poison, victims do not associate the bait with the symptoms.

Indeed, the older anticoagulants such as warfarin have such relatively low toxicity that ingestion of a lethal dose requires the victim to feed on poisoned bait on several successive days. Different rodent pest species have very different levels of susceptibility to warfarin (Greaves, 1985), but luckily the cosmopolitan pest R. norvegicus is one of the most susceptible. Warfarin is still the most widely used anticoagulant and also one of the cheapest. In a study of rodent damage to stored food in Cuba where losses were low to start with (about 1%) Hernandez and Drummond (1984) found that a cost to benefit ratio of from 1:22 to 1:185 was achieved in all 11 trial warehouses. Of course, such large benefits are only achieved in a well-planned and carefully executed control programme where appropriate levels of warfarin bait are maintained.

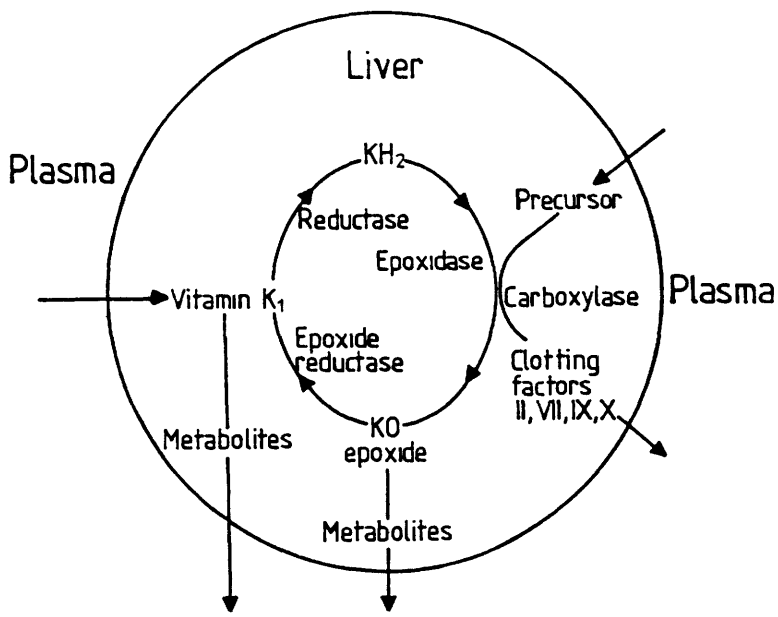

Fig. 1. The vitamin K_1 epoxide cycle in the mammalian liver.

Because warfarin and other anticoagulants developed in the 1950s ('first generation') were so successful, it came as a major blow when resistance to warfarin and some other anticoagulant rodenticides was recorded in R. norvegicus, in Scotland in 1958 (Boyle, 1960). In retrospect, the development of resistance was not surprising since use of rodenticides gives a high selective advantage to any resistant individual. Resistance in R. norvegicus is generally the expression of a single major gene, subject to effects of some modifier genes and phenotypically dominant to the normal, susceptible allele (Greaves and Ayres, 1967, 1969).

Resistant individuals have a vitamin K_1 epoxide reductase with a reduced affinity for both vitamin K_1 and warfarin; warfarin in effect does not disrupt the vitamin K_1 cycle in resistant genotypes, but the reduced affinity for vitamin K_1 does present the rat with physiological problems. In order to drive the cycle adequately, resistant heterozygotes need two or three times and resistant homozygotes nearly 20 times the amount of vitamin K_1 required by susceptible homozygotes (Bishop, 1981). Warfarin metabolism is discussed by Hermodson et al., (1969), and the mechanism of resistance by Bell and Caldwell (1973), Zimmerman and Matschiner (1974) and MacNichol (1986). The pleiotropic manifestations of resistance have a profound effect on population genetics and resistance management, as will be shown later.

Warfarin Resistance and Attempts at Management

Inherited resistance to normal control levels of warfarin was first detected in R. norvegicus in the United Kingdom (Boyle, 1960; Drummond, 1966). Resistance in both M. musculus (Dodsworth, 1961) and R. rattus (Greaves et al., 1973) was also confirmed by 1970. In the U.S.A., resistance was not discovered until 1971 (Jackson and Kaukeinen, 1972) though it would be surprising if it had not been present much earlier; in Europe outside the United Kingdom, resistance in R. norvegicus was found in Denmark in 1962-63 (Lund, 1964), Holland in 1966 (Ophof and Langeveld, 1969) and Germany in 1968-69 (Telle, 1972). In R. rattus, resistance has also been detected in the U.S.A. (Jackson and Ashton, 1980), India (Deoras et al., 1972), Japan (Meehan, 1984) and Australia (Saunders, 1978). There is also evidence of resistance in various non-commensal field pests (Meehan, 1984). Meehan (1984), Lund (1984) and Greaves (1985) provide the most recent reviews of the subject. The extent of the problem is almost certainly underestimated because of inadequate monitoring. Greaves (1986) reviews practical attempts to manage resistance in Britain and we shall only give a brief summary here. Some theoretical aspects of management are discussed in the next section.

1. Eradicating new outbreaks of resistance

Drummond and Rennison (1973) describe procedures used to detect new outbreaks of resistance. Official policy in the United Kingdom was to exterminate the resistant rats with acute poisons, and in seven out of eleven cases the method seemed to work though it is not certain that inherited resistance was present in all cases. A major problem is the time delay of perhaps one or two years between development and detection of resistance (Drummond 1970, 1971), and the spread of resistant animals from the focus. Eradication with acute poisons seems to have worked in Holland (Ophof and Langeveld, 1969).

2. Eradicating widely established resistance

Attempts to eradicate the Welsh population of resistant R. norvegicus in the early 1960s were unsuccessful (Bentley and Drummond, 1965). Greaves (1986) suggests that perhaps the objective of eliminating all rats in an area of five square miles was inappropriate and that modern alternative rodenticides would increase the chances of success. Resistance monitoring and early action are clearly of paramount importance.

3. Containment of resistance

Another approach adopted in Britain in the 1960s was to establish a rat-free perimeter zone around the focus of resistance, again using acute poisons (Drummond, 1966). The approach was found to have failed within two years of adoption (Pamphilon, 1969), possibly because the extent of resistance was underestimated initially.

4. New rodenticides

There are alternatives to anticoagulant rodenticides, but most alternatives are less satisfactory for reasons such as instability, unpalatability, non-target hazards or price. Some anticoagulants developed in the 1970s ('second generation') have excellent properties for example difenacoum, bromadiolone, brodifacoum and flocoumafen, though they may be relatively expensive. However, cross-resistance to difenacoum has already developed in the United Kingdom (Redfern and Gill, 1978) and may become an eventual problem with all anticoagulant compounds, unless simple resistance to warfarin can be detected and eliminated rapidly.

5. Resistance Monitoring

The key to practical resistance management is adequate monitoring. The first sign of resistance is failure of control of control but there may be many reasons other than inherited resistance for control failure. Confirmation of suspected resistance requires live animals to be captured, fed warfarin, and held under controlled conditions for some days before a blood sample is taken for measurement of clotting ability (Greaves et al., 1977). The procedure requires facilities and expertise which are rarely available and poses considerable health and safety problems.

Monogenic resistance as found in R. norvegicus could in theory be detected in samples of liver if an antibody were developed to the mutant vitamin K_1 reductase. However, the enzyme is membrane-bound (MacNichol, 1986) and therefore has not been isolated, a necessary first step in production of a specific antibody. It is quite possible to develop a DNA probe which could detect specific resistance mechanisms in tissue samples from dead animals sent through the post to an appropriate laboratory. We have an

experimental protocol which would allow development and testing of such a probe within two to three years (C.J. Skidmore and R.H. Smith, unpublished), but so far we lack the funds to pursue the project.

Population Genetics of Resistance in Rattus norvegicus

The dynamics of genes associated with resistance in populations depend on the fitnesses of different genotypes, which may be frequency dependent or density dependent or both, the mating system of the species, and migration into and out of a population. Resistance is not always genetically simple, but in R. norvegicus and M. musculus seems to be largely determined by a single autosomal gene (Greaves and Ayres, 1967; Wallace and MacSwiney, 1976). We will use the symbol R to denote the resistant allele and S to denote the susceptible allele.

1. Heterozygous advantage

Inherited resistance to first generation anticoagulants such as warfarin became established and spread simply because resistant genotypes were given a strong selective advantage (they survived, other genotypes died) when such poisons were used. As noted in the introduction, however, there is a cost associated with resistance; heterozygotes (RS) need two to three times and resistant homozygotes (RR) nearly 20 times the amount of vitamin K_1 required by normal, warfarin-susceptible homozygotes (SS). Even when reared in the sheltered conditions of an animal house, there is some suggestion that the resistant homozygous genotype is severely deleterious (Bishop et al., 1977; Bishop, 1981) and young males (up to eight weeks old) seem to suffer more than young females. Inability to produce clotting factors at normal levels of intake of vitamin K_1 means that females are unlikely to survive haemorrhage when giving birth if they are homozygous resistant RR. In the wild, the cost of being resistant is likely to be greater than in the laboratory, since an active life outside a cage will inevitably lead to more internal haemorrhaging. It has been suggested that strong selection against resistant (vitamin K_1 deficient) and susceptible (prone to poisoning) homozygotes leads to a balanced polymorphism maintained by heterozygous advantage (Greaves et al., 1977), if warfarin is used. Under this assumption, Greaves et al.,(1977) and Partridge (1979) were able to estimate the relative fitnesses of genotypes in the presence and absence of warfarin treatment (Table I).

The estimates in Table I are made from data on changes in phenotype frequencies, assuming random mating (Hardy-Weinberg equilibrium). If the two assumptions (random mating and heterozygous advantage) are true, then there will be an equilibrium allele frequency of 0.66 susceptible (S) and a phenotypic frequency of 0.44 susceptible (SS). Deterministic predictions of gene frequency changes in the presence and in the absence of warfarin are shown in Figs. 2a and 2b.

TABLE I

Relative fitnesses of the three genotypes with and without warfarin

	Genotypes		
Conditions	RR	RS	SS
Warfarin used	0.37	1.00	0.68
Warfarin not used	0.46	0.77	1.00

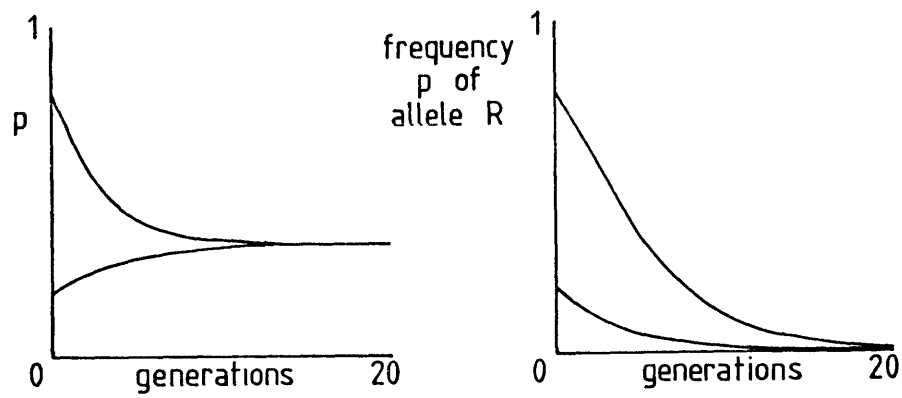

Fig. 2. Simulated gene frequency changes based on the fitnesses in Table I: (a) warfarin used, (b) warfarin not used.

The practical conclusion from these models is that the physiological cost of warfarin resistance may be exploited in order to manage resistance. By removing warfarin selection against susceptible genotypes, the S allele is favoured and the R allele will slowly decline in frequency, a prediction supported by two independent studies in Britain (Greaves et al., 1977; Partridge, 1979). This approach, however, provides little comfort for the farmer who must either suffer the depredations of the rats or fall back on the older, less efficient, acute rodenticides, unless the resistant rats may be dealt with by other means.

2. Resistance and cross-resistance to anticoagulants

The increasing prevalence of resistance during the 1960s gave rise to renewed interest in rodenticide development. Resistance to warfarin extended to other first generation anticoagulants then available, though coumatetralyl had a useful level of activity until eventually cross-resistance was found (Meehan, 1984). A number of so-called 'second generation' anticoagulants have since been introduced, the first of which was the highly successful compound difenacoum (Hadler et al., 1975); difenacoum was found to be active against resistant animals, though less toxic to them than to susceptibles. However, cross-resistance to difenacoum has now been found in all three commensal species (Lund, 1984; Redfern and Gill, 1978; Rowe and Bradfield, 1976). An area around Basingstoke, Hampshire (in England) has a population of R. norvegicus largely resistant to both warfarin and difenacoum. The cross-resistance, though, seems to be recessive (mainly expressed in the resistant homozygote; Greaves et al., 1982).

The practical implication of recessive resistance to difenacoum is that, although the phenotypic frequency of resistance may not appear significant for many generations, once resistance reaches a detectable level, the frequency of the R allele will be high and resistance will be difficult to eliminate.

Currently, there are available other second generation anticoagulants such as bromadiolone, brodifacoum and flocoumafen which are effective against even the Hampshire resistant rats. However, it may only be a matter of time before resistance evolves to the newer compounds, perhaps by polygenic modification of expression of the major gene that determines warfarin resistance.

3. Permanent bait points, the economic threshold and knowing when to stop

Because rodenticides are applied at bait points near to but not in direct contact with the stored products, it is possible to keep bait points permanently topped up with rodenticide as a kind of insurance policy against rodent invasion. Unfortunately, permanent bait points prevent natural selection acting in favour of susceptible genotypes (which are liable to be poisoned), and the frequency of resistance must inevitably rise until an equilibrium is reached (either fixation, or some intermediate frequency if there is heterozygous advantage). Therefore permanent baiting is to be avoided immediately it ceases to be fully effective, else the medium to long term cost will be the spread of resistance.

The alternative is to use anticoagulant rodenticides only when there is a significant rodent problem, that is when rodent damage exceeds some perceived economic threshold. Because anticoagulant resistance carries with it a physiological cost, resistance will therefore tend to decline in frequency when rodent numbers are below the economic threshold density. The decline in frequency occurs

because of a general debilitating effect of haemorrhage, and probably specific effects on females during pregnancy and parturition and on males when competing directly for social position and access to mates. During a period of population increase, not only will susceptible genotypes contribute relatively more to that increase, but the debilitating effects of haemorrhage in resistant homozygotes are likely to be heightened as agonistic interactions also increase with density. Hence the frequency of resistant alleles will fall, until the application of anticoagulant rodenticide begins to kill susceptible genotypes (Fig. 3).

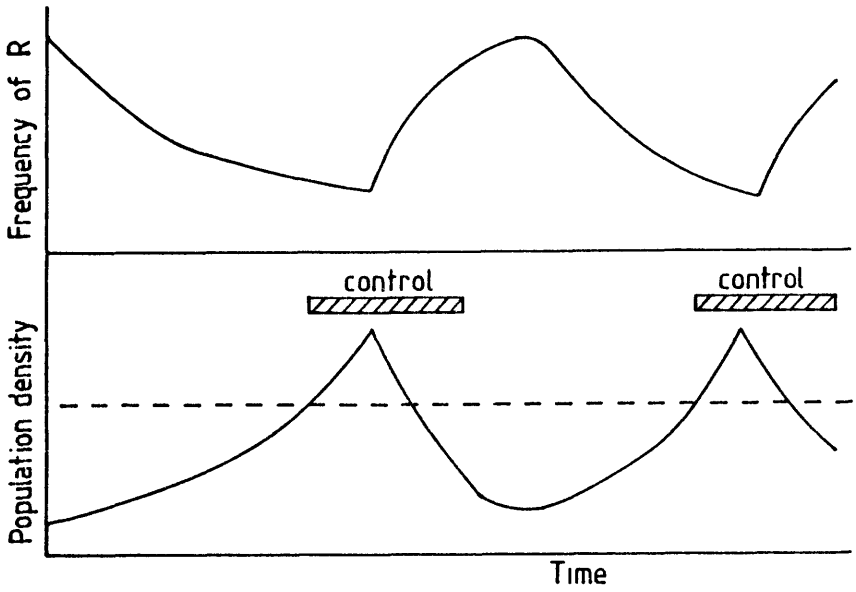

Fig. 3. Control is initiated when population density and damage exceed some threshold (dashed line). The frequency of resistant R alleles is expected to fall and rise in inverse relation to population density.

Clearly, the level to which the frequency of the resistant allele rises will depend on the proportion of susceptible genotypes killed. Control failure is how resistance is first detected, and a properly monitored control programme where bait is offered in increasing amounts until bait-take begins to decline will indicate resistance if bait-take stays at a high level. If resistance is to be contained, it is essential to stop using the anticoagulant rodenticide when resistance is detected. Ideally, treatment should

be completed using a different poison or a sterilising agent in order to prevent resistant survivors from breeding (see next section).

4. Population dynamics, social behaviour and the potential for chemosterilants

It was suggested in the previous section that the deleterious pleiotropic effects of resistance vary with population density. Some support for this idea comes from the work of Kendall (1982) who found that resistant homozygotes survived extremely well in a low-density farm population, following warfarin treatment. Experience suggests that populations of R. norvegicus on farms may fluctuate around acceptably low levels perhaps for years, but then erupt to a level where rat numbers and damage levels become unacceptably high. It seems that space may be the main limiting factor in R. norvegicus, and that animals are competing more for predator-free space than for food. Hence, we can imagine a low density equilibrium maintained by failure to breed, forced emigration and predation rather than by shortage of food (Fig. 4). When a population exceeds some threshold level or breakpoint, for whatever reason, social control breaks down, immigrants move in and breed, predators cannot control the increase in numbers and population density rises towards an equilibrium level where food supply is the limiting factor. Telle's (1966) work supports the concept of a lower equilibrium maintained by social behaviour; at low density, rats recognise individuals in a population and repel immigrants while at high density they are unable to recognise everyone and there is much migration in and out with high levels of agonistic interaction. The relative fitness of resistant homozygotes must inevitably be lower, and natural selection will operate most strongly against resistant genotypes when numbers move towards the higher equilibrium; it is ironic that, if Fig. 4 has any validity, the population level at which natural selection is most effective against resistance is that where rodenticidal control must be implemented, hence favouring resistance.

There is a potential practical application of population control through social behaviour. If resistant survivors of a control treatment could be sterilised, their presence would tend to repel immigrant intruders (see also Smith, 1984) and yet they would not increase the numbers of resistant animals. Currently, only one chemosterilant is marketed; the compound alpha-chlorohydrin kills a proportion of both male and female rats and sterilises about half of the remaining males (reviewed by Ericsson 1982). However, there is considerable research on human male reproductive inhibitors and there must be many experimental compounds which, though unsuitable for human use for reasons of safety, could be suitable for rodents. The use of a chemosterilant to mop up resistant survivors at the end of an anticoagulant treatment could therefore provide an important weapon in the fight against resistance in the future, but unfortunately there is little commercial interest in their development at present.

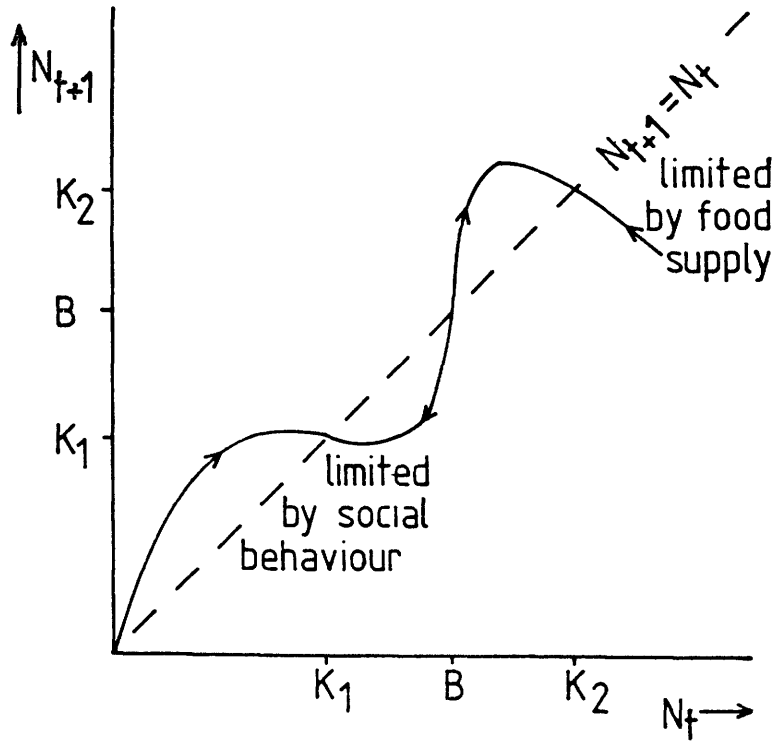

Fig. 4. Postulated relationship between numbers in one generation N_{t+1} and numbers in previous generation N_t. An equilibrium population size is defined wherever the curve crosses the dashed line ($N_{t+1} = N_t$). The lower and upper equilibria are stable, the middle equilibrium is unstable (a breakpoint).

Conclusions

Greaves (1986) stressed that the only way to reduce the frequency of resistance to an acceptable level is to place resistant individuals at a selective disadvantage. Natural selection ought to reinforce this general approach since resistance alleles are usually deleterious in the absence of pesticide. In practice, natural selection may be ineffective because the initiation of control (when rat numbers are high) and the duration of treatment (longest when resistance is present but unsuspected) both act strongly in favour of resistance. The useful life of rodenticides could be lengthened if resistance was adequately monitored and use of anticoagulants promptly ceased in resistant populations. Although there are

alternatives to anticoagulants, their cost and relative effectiveness generally mean that they are best reserved for use against infestations containing resistant individuals and against potentially resistant survivors of anticoagulant treatment.

Monitoring resistance is the major problem in effective management. At present, resistance tests are difficult and expensive. Use of DNA technology offers an effective alternative to trapping and holding wild rodents, but a DNA probe, though practically feasible, has not yet been developed.

We have not discussed one of the most difficult aspects of resistance management: how to manage and to organise management (Greaves, 1986). Inherited resistance can only be dealt with effectively if there is the will to look beyond immediate economic aspects and towards medium and long term problems. It may often be cheaper in the short term to carry on using warfarin when it is becoming less effective than to change to a better but more expensive alternative, and alternatives may not be readily available in some places. Taking a view of resistance that goes beyond the current year's profits may understandably have little appeal to the farmer or store manager, and government agencies and industry must be willing to take on responsibility for long term strategies of resistance management even when there is a short term financial cost.

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