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THE DISTRIBUTION AND SIGNIFICANCE OF ANTICOAGULANT-RESISTANT NORWAY RATS (*RATTUS NORVEGICUS*) IN ENGLAND AND WALES, 1988-95

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ABSTRACT: Between 1988 and 1995 populations of rats on agricultural premises were sampled to investigate the distribution of anticoagulant-resistant rats in England and Wales. In total, approximately 1,670 rats from 115 locations were tested for resistance to warfarin. Rats that were warfarin-resistant were subsequently tested for resistance to difenacoum, and since 1991 for resistance to bromadiolone. In some cases rats were also tested for resistance to brodifacoum, and in 1995 for resistance to flocoumafen. The results of these tests showed that there was a high prevalence of resistance to the first-generation anticoagulant, warfarin, in several regions of England and Wales. Rats from most populations sampled since 1991 appeared to be more resistant to bromadiolone than difenacoum, but in central southern England there were some populations where the reverse was true. In this same part of the country there was a relatively small focus where the rats had high degrees of resistance to several anticoagulant rodenticides. There was little evidence of resistance to brodifacoum or flocoumafen. The data are discussed with respect to the impact of anticoagulant rodenticide resistance on control of rats in the United Kingdom.

KEY WORDS: anticoagulants, brodifacoum, bromadiolone, commensal rodents, difenacoum, flocoumafen, laboratory testing, Muridae, Norway rats, rats, resistance, Rodentia, rodenticides, rodents, U.K., vertebrate pest control, warfarin

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INTRODUCTION

Norway rats (*Rattus norvegicus*) resistant to the anticoagulant rodenticide warfarin were first discovered on a pig farm in Scotland in 1958 (Boyle 1960). Subsequently, populations of rats resistant to warfarin and other first-generation anticoagulant rodenticides were discovered in Denmark (Lund 1964), England and Wales (Drummond and Bentley 1967), Germany (Telle 1967), Holland (Ophof and Langeveld 1969), the United States of America (U.S.A.)(Jackson and Kaukeinen 1972) and Italy (Alessandroni et al. 1980). A second generation of anticoagulant rodenticides was developed (reviewed by Hadler and Buckle 1992) to overcome the control problems caused by resistance to the first-generation compounds. The newer anticoagulants such as bromadiolone and difenacoum were based on the same chemical structure and mode of action as warfarin. With the benefit of hindsight, it is not surprising that resistance was discovered within a few years of the first commercial use of difenacoum (Redfern and Gill 1978). Further studies (Greaves et al. 1982) indicated a significant and widespread incidence of difenacoum-resistant rats across an area of central southern England with a history of warfarin resistance in rats. Populations of rats that included individuals resistant to bromadiolone have been reported in Denmark (Lund 1981), Holland (Van Blaaderen and Bode 1989) and Germany (Pelz et al. 1995). Responses to a questionnaire indicated that laboratory tests have identified populations of Norway rats in Denmark, France, Germany and the United Kingdom (U.K.) that were resistant to one or more anticoagulant rodenticides (Myllymaki 1995). That same report indicated that *Rattus norvegicus* trapped and tested in Finland were susceptible to anticoagulant rodenticides.

The authors' laboratory has been funded by the U.K. Ministry of Agriculture, Fisheries and Food to investigate the occurrence and significance of anticoagulant-resistant rats in England and Wales. Historical data (Drummond 1966; Greaves 1970; MacNicoll and Gill 1987) indicated that warfarin-resistant rats predominated in most rat populations in Wales and the bordering English counties, southeast England, central southern England, and central Scotland (Figure 1). The present paper reports the results of tests carried out between 1988 and 1995 for resistance to warfarin, difenacoum, brodifacoum, bromadiolone (1991 to 1995 only) and flocoumafen (1995 only). Sampling of rat populations was based largely on reports of poor or unsuccessful control using anticoagulant rodenticides, and is, therefore, biased towards detection of anticoagulant-resistant rats. In addition, samples of some rat populations were tested for anticoagulant resistance prior to field studies designed to investigate the causes of control failure (Quy et al. 1992a, 1992b, 1994; Cowan et al. 1995).

METHODS

Animals

Rats were sampled from infestations on agricultural premises using single-capture live traps, and transported to the laboratory. They were treated with insecticide to reduce ectoparasite infestation, and housed singly in suspended wire cages. They were fed rat and mouse No. 1 low vitamin K (<1 mg/kg of vitamin K) pelleted diet (SDS Ltd., Witham, Essex, U.K.) ad libitum, and provided free access to water containing 100 mg/L of menadione sodium bisulphite (MSB; Sigma Chemical Co., Poole, Dorset, U.K.) to prevent vitamin K deficiency.

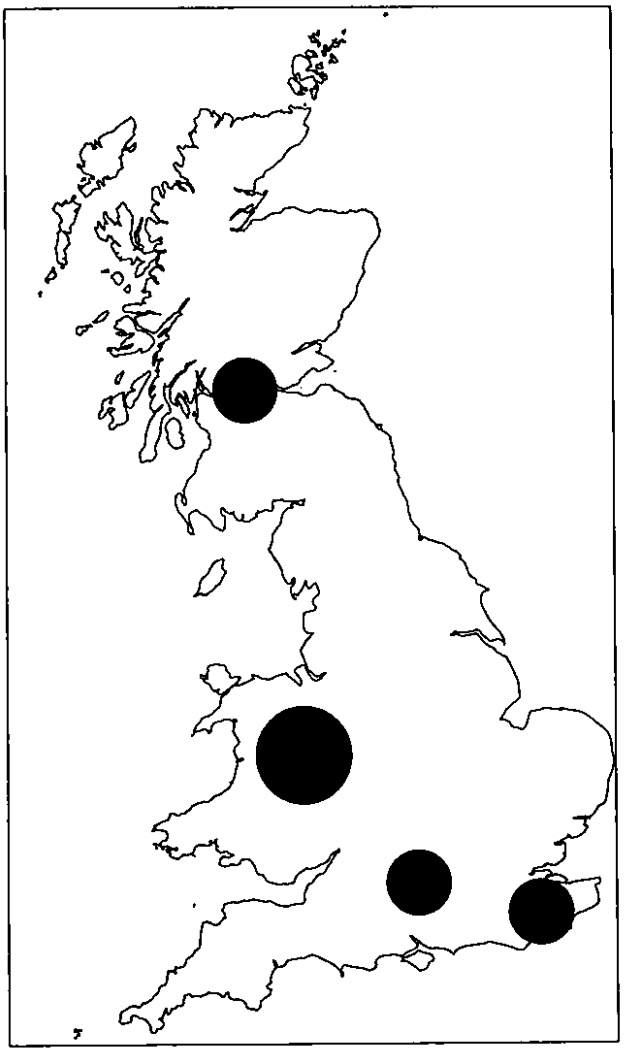


Figure 1. Location of populations of warfarin-resistant rats in the U.K. 1958 to 1987.

Testing for Anticoagulant Resistance

Between 1988 and 1991, warfarin resistance status was determined using the method of Martin et al. (1979). From 1992 onwards a revised method was used, which incorporated several refinements (MacNicoll and Gill 1993). Animals that were warfarin-resistant were, after a gap of at least one week, tested for resistance to difenacoum. Warfarin-susceptible rats were not usually subjected to further tests for anticoagulant resistance.

In 1988 and 1989, resistance to difenacoum was determined by survival of a five-day feeding test using 0.005% (w/w) difenacoum (Redfern and Gill 1978), and since 1990 by blood clotting response (BCR) four days after administration of a sub-lethal dose of difenacoum (Gill et al. 1993). From 1991 onwards warfarin-resistant rats were tested for resistance to bromadiolone by BCR test (Gill et al. 1994). There were gaps of at least three weeks between sequential tests for resistance to second-generation anticoagulants on the same animal.

Difenacoum (or bromadiolone from 1991 onwards) resistant rats were subjected to a seven-day feeding test using 0.0005% (w/w) brodifacoum in the diet (Gill and MacNicoll 1991). Rats that survived for more than three weeks after the end of the feeding regime had at least a low degree of resistance to brodifacoum.

In 1995 rats that had a degree of resistance to difenacoum and/or bromadiolone were tested for resistance to flocoumafen. Full details of this test will be published elsewhere. Flocoumafen (0.6 mg/kg body weight) was administered by oral intubation in conjunction with 10 mg/kg body weight of MSB. Proteolytic activity of blood clotting Factor X was measured four days later, and rats with greater than 0.1 units of Factor X per ml of plasma were classified as flocoumafen-resistant. Factor X levels in control animals were approximately 0.5 units per ml of plasma.

Mapping of Anticoagulant Resistance in England and Wales

The grid reference for each farm where rats were trapped between 1988 and 1995 was recorded. The results of warfarin resistance tests were used to determine whether <10%, 10 to 90%, or >90% of rats sampled from each location were warfarin-resistant. This information was entered, together with grid references, into a software package (DMAP for Windows, Alan Morton, Imperial College, London, U.K.) to provide the distribution map shown in Figure 2.

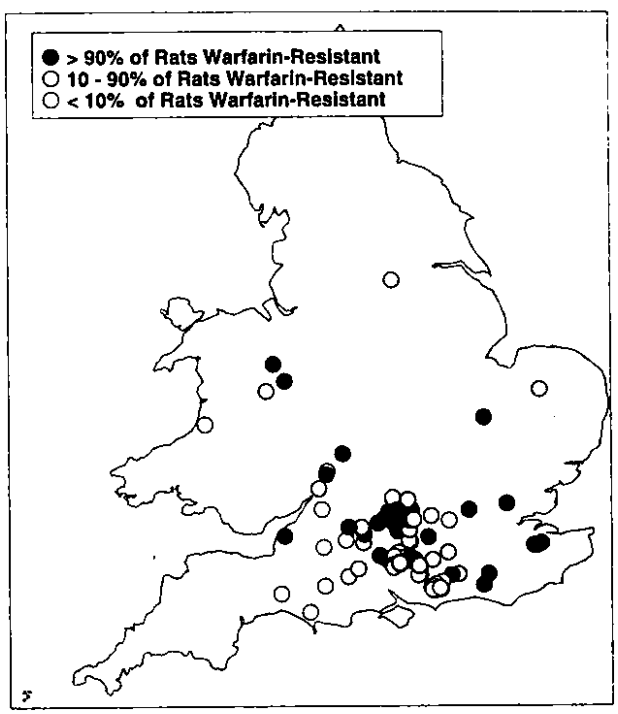


Figure 2. Location of rat populations sampled between 1988 and 1995 and tested for resistance to warfarin.

Figure 3a was produced in a similar manner, but each site sampled in 1988 and 1989 was categorized on the basis of <10%, 10 to 50%, or >50% of rats in each sample surviving a difenacoum feeding test. Figure 3b shows the results from 1990 to 1995, but in this case farms were categorized on the basis that the mean percentage clotting activity (PCA) on day 4 of BCR tests for difenacoum resistance was <10%, 10 to 50%, or >50% of activity measured at the time of difenacoum administration.

Figure 4 plots the distribution of brodifacoum resistance based on survival of a feeding test. Each location was categorized on the same basis as survival of a difenacoum feeding test in Figure 3a. The results of BCR tests for bromadiolone resistance between 1991 and 1995 were categorized on the same basis as for difenacoum resistance in Figure 3b, and are presented in Figure 5.

RESULTS AND DISCUSSION

Warfarin Resistance

Figure 2 summarizes the results of warfarin resistance tests carried out on 1,670 rats trapped on 115 farms between 1988 and 1995. The symbol at each location indicates that <10% (30 farms; open circles), between 10 and 90% (38 farms; shaded circles), or >90% (45 farms; filled circles) of the sample were warfarin-resistant. These groups were selected to highlight populations that contained few, if any, warfarin-resistant rats, and those where use of anticoagulant rodenticides had selected populations that included few, if any, susceptible rats. This enables identification of areas where warfarin (and other first-generation anticoagulant rodenticides) could be successfully used for control of rats because of the predominance of warfarin susceptibility. Conversely, predominance of warfarin-resistant rats indicates that the first-generation compounds would probably not be effective. Some success may be achievable in control of intermediate populations using warfarin, but the likelihood of further selection of higher degrees of anticoagulant resistance should influence the choice of active ingredient used.

It can be seen from Figure 2 that there are large areas of the U.K. where we have not sampled rat populations for warfarin resistance testing. Since the survey has been largely responsive to reports of rat control problems, and relies on the presence of relatively large infestations of rats, it is suggested that first-generation anticoagulants, such as warfarin, can be successfully used for control of rats on agricultural premises in more than 50% of the land area of England and Wales. Neither the authors' laboratory, nor any other organization, has routinely sampled rats from urban areas in the U.K. for the purposes of resistance testing. Reports of rat control problems in urban areas are not routinely investigated, and only two samples of rats have been subjected to laboratory tests for resistance. It is, therefore, difficult to comment on whether anticoagulant resistance is currently a serious problem in urban areas of the U.K.

The data in Figure 2 show, however, that many populations of rats in rural areas of central southern and southeast England included significant numbers of warfarin-resistant individuals. It is also interesting to note that some samples of rat populations that included warfarin-resistant individuals were from locations (Figure 2) remote from the known foci of resistance (Figure 1). This may indicate that warfarin-resistant rats have been transported to those farms from other parts of the country. Alternatively, warfarin-resistant rats may have been common in neighboring populations, but effective control was achieved with second-generation anticoagulant rodenticides and problems were not, therefore, reported.

Difenacoum Resistance

The results of testing 909 warfarin-resistant rats for resistance to difenacoum between 1988 and 1995 are shown in Figure 3. In 1988 and 1989 difenacoum resistance was determined by survival of a feeding test (Redfern and Gill 1978), and the results in Figure 3a for 11 locations (183 rats) are grouped on the principle that <10 % (3 farms; open circles), 10 to 50% (7 farms; shaded circles), or >50% (1 farm; filled circles) of rats survived.

The new BCR test for difenacoum resistance (Gill et al. 1993) used from 1990 onwards had a number of advantages over the feeding test, including the possibility of testing difenacoum-susceptible animals for resistance to bromadiolone and other anticoagulants. The authors have grouped the results for 79 locations shown in Figure 3b into those samples where the mean PCA value of all (warfarin- resistant) rats tested was <10% (23 farms; open circles), between 10 to 50% (35 farms; shaded circles), and >50% (21 farms; filled circles). The data presented by Gill et al. (1993) showed that rats with PCA values of <10% on day 4 after administration of difenacoum were unlikely to survive feeding on 0.005% (w/w) difenacoum for five days, and that when PCA values were 50% then >50% and >70% of male and female rats survived, respectively. Using mean PCA values for population samples can be criticized on the grounds that BCR may not have been normally distributed within the sample, and the mean values were not, therefore, wholly representative. The only method to fully illustrate the data would be to use histograms of the results of BCR tests on rats from each location. Mean PCA values do, however, reflect the distribution of BCR within the sample. By dividing the samples into three broad categories the authors believe that this is the best means of concisely presenting the data. Thus, the three categories illustrated in Figure 3b could be considered as locations where difenacoum-susceptible rats predominated, where some rats in the population had a low degree of resistance to difenacoum, or where they had a high degree of resistance to difenacoum.

Difenacoum-resistant rats were first identified in central southern England (Redfern and Gill 1978; Greaves et al. 1982), and it was from this area that rats were sampled which had the highest degrees of difenacoum resistance. Several factors have been identified (Quy et al. 1992a, 1992b) that may have detrimental effects on control of rats on farms in central southern England, but there is evidence of selection pressure favoring difenacoum-resistant rats (Cowan et al. 1995). That same report also concluded that control of these rats with difenacoum did not represent a practical problem, although that was based on trials carried out on farms

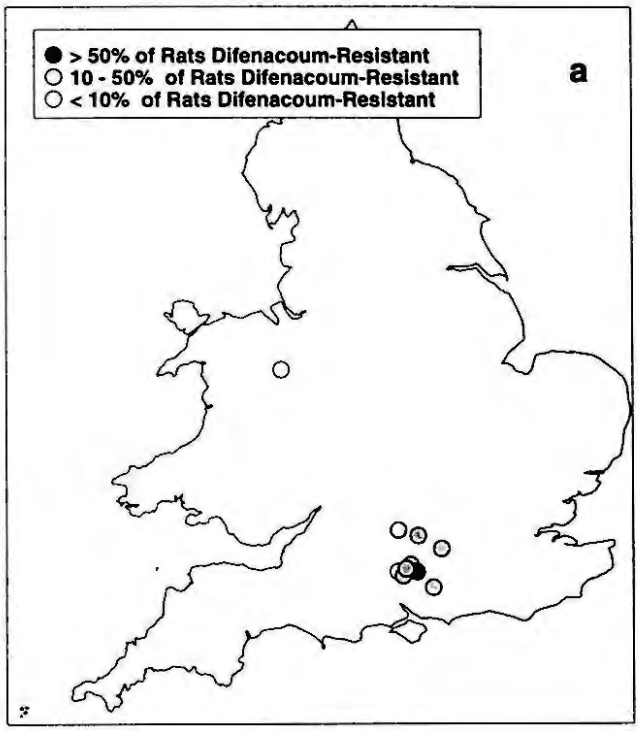


Figure 3a. Location of rat populations sampled between 1988 and 1989 and tested for resistance to difenacoum by feeding 0.005 (w/w) difenacoum for five days (Redfern and Gill 1978).

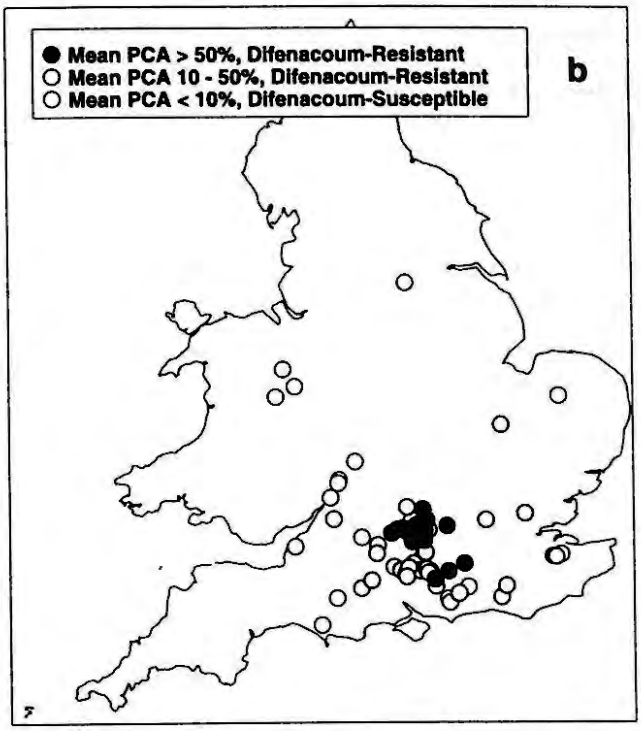


Figure 3b. Location of rat populations sampled between 1990 and 1995 and tested for resistance to difenacoum by blood clotting response to sub-lethal dose of difenacoum (Gill et al. 1993).

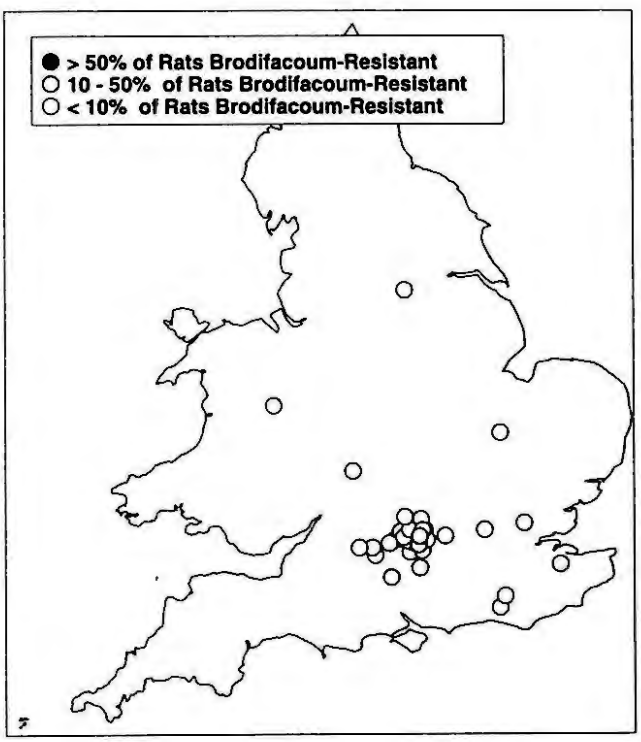


Figure 4. Location of rat populations sampled between 1988 and 1995 and tested for resistance to brodifacoum.

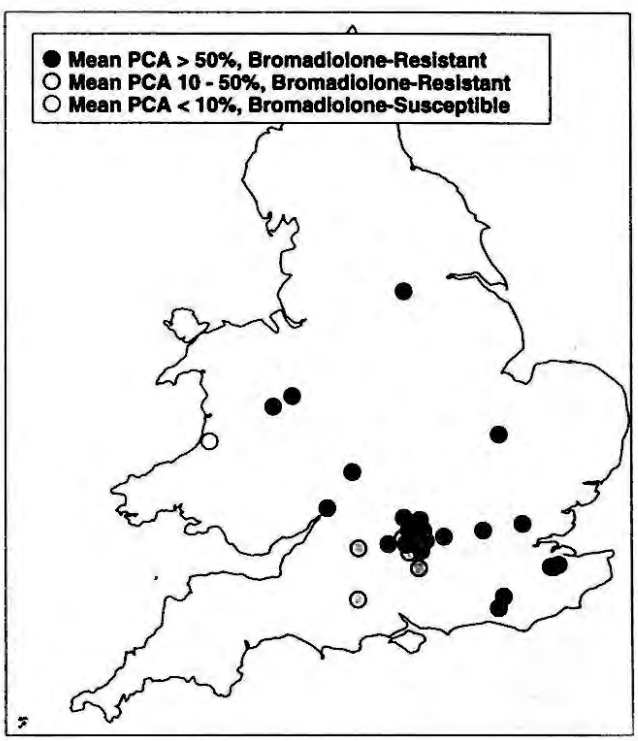


Figure 5. Location of rat populations sampled between 1991 and 1995 and tested for resistance to bromadiolone.

with rat populations within the category of a low degree of resistance to difenacoum. Figure 3b indicates that rats with the highest degrees of resistance to difenacoum were in the north of this area, where resistance may have a greater influence on the outcome of rat control on farms. Outside of central southern England it would appear that rats on agricultural premises are susceptible, or at worst have only a low degree of resistance, to difenacoum.

Brodifacoum Resistance

The data presented in Figure 4 summarize the results of brodifacoum resistance testing of 462 difenacoum or bromadiolone-resistant rats in 41 samples of farm rat populations trapped between 1988 and 1995. The results were categorized as <10% (37 farms; open circles), or 10 to 50% (4 farms; shaded circles) of rats surviving a brodifacoum resistance feeding test.

Figure 4 shows that samples from most farms contained <10% of individuals that were resistant to brodifacoum, even though those rats were difenacoum or bromadiolone-resistant, indicating that infestations should be successfully controlled with brodifacoum. Significant numbers of brodifacoum-resistant rats were only detected on four farms in a relatively small area of central southern England. Unfortunately, the authors have not been able to carry out field trials with brodifacoum in that area, and cannot assess the impact of an apparently low degree of brodifacoum resistance on control success or failure.

Bromadiolone Resistance

Between 1991 and 1995, approximately 600 warfarin-resistant rats were tested for bromadiolone resistance using a BCR test (Gill et al. 1994). The samples of rats from 41 locations shown in Figure 5 were categorized as described above for Figure 3b, i.e., locations where the mean PCA value for the sample was <10% (1 farm; open circles, bromadiolone-susceptible), between 10 to 50% (11 farms; shaded circles, a low degree of bromadiolone resistance), and >50% (29 farms; filled circles, a high degree of bromadiolone resistance).

This is the first time that widespread sampling of rats has been carried out in the U.K. for the purpose of bromadiolone resistance testing. The data in Figure 5 show that warfarin-resistant rats trapped from populations in different parts of England and Wales also had high degrees and/or high prevalence of resistance to bromadiolone. The population of bromadiolone-susceptible rats sampled in west Wales were the warfarin-susceptible rats tested to validate the BCR test (Gill et al. 1994). In central southern England some samples of rats were categorized as including rats with a low degree of bromadiolone resistance. This corresponds to locations where the rats also had low degrees of resistance to difenacoum.

A field trial on a heavily rat-infested farm in central southern England showed that a 23-day control program using surplus baiting with 0.005% (w/w) bromadiolone had little impact on the size of the population (Quy et al. 1995). Rats that had survived this treatment were sampled by trapping, and bait label analysis indicated that 51% (n=63) had eaten more than 100 g of bait. Laboratory tests showed that the rats had a high degree of resistance to bromadiolone, and it was concluded (Quy et al. 1995) that the study provided the first unequivocal demonstration of control failure with a multiple-feed second-generation anticoagulant that was attributable to resistance. The BCR of rats sampled from farms within a few miles of the study site indicated that they also had high degrees of resistance to bromadiolone, which suggests that it may also have been difficult to control rats on neighboring farms with bromadiolone.

Flocoumafen Resistance

Use of a new BCR test for flocoumafen resistance began in 1995. Of the 159 difenacoum and/or bromadiolone-resistant rats from 14 locations tested for flocoumafen resistance, only two samples, from central southern England, included rats that had resistance to flocoumafen. In one sample only 1/9 rats tested had a low degree of resistance to flocoumafen. All six female rats and 3/10 male rats tested from a second farm apparently had significant degrees of resistance to flocoumafen.

Cross-resistance to More Than One Anticoagulant Rodenticide

The testing regime used in the laboratory begins with testing for resistance to warfarin, as a representative of the first-generation anticoagulant rodenticides. The results of many studies over the last 20 years have shown that warfarin-susceptible rats are susceptible to the whole group of anticoagulant rodenticides. The results presented in this paper indicate that 27% (21/79) and 71% (29/41) of populations of warfarin-resistant rats sampled included rats that had high degrees of resistance to difenacoum or bromadiolone, respectively.

Only 12 samples from central southern England (e.g., the study site used by Quy et al. 1995) included rats that had a high degree of resistance to both difenacoum and bromadiolone. Some of those rats also had a low degree of resistance to brodifacoum. Apart from in this small area, it should be possible to achieve control of warfarin-resistant rats using difenacoum or bromadiolone as appropriate, especially where the rats have only a low degree of resistance to these rodenticides. Nevertheless, the possibility of selecting higher degrees of resistance to anticoagulants should not be ignored.

Although there is no published test for resistance to diphacinone, 11 warfarin-resistant rats were tested in one sample from central southern England by feeding 0.005% (w/w) diphacinone for five days without alternative food. Ten of the rats survived more than three weeks after the end of the feeding period, each having eaten more than 85 g of the diet containing diphacinone. The farmer had been using a bait containing the same concentration of diphacinone in an attempt to control rats on his farm, but the authors' results indicate that those attempts were unlikely to be successful.

Temporal Changes

Although the authors' laboratory has been monitoring resistance to anticoagulant rodenticides in England and Wales for 30 years, it is not possible to make significant conclusions on temporal changes. Most apparent changes in resistance status arise following the introduction of a

new compound, application of a new test or sampling of rats from a new area. Early studies indicated that migration of warfarin-resistant rats, and continued selection, resulted in an apparent radial distribution of three miles per year from a focus of resistance (Drummond 1966). If the results of the present study are compared to earlier reports (Greaves et al. 1982), it is clear that the already extensive distribution of difenacoum-resistant rats in central southern England has not increased by three miles a year in any direction over the last 12 to 15 years. Studies are in progress to assess the deleterious effects of anticoagulant resistance genes on the fitness of rats in this area, which may help explain why they have not apparently spread further afield. Alternatively, there may be ecological factors in the area that favor large rat infestations requiring frequent control with anticoagulant rodenticides, which causes heavy selection pressure towards anticoagulant resistance.

Future Work

In 1995 the authors' changed their tactic for selection of rat populations to be sampled up to 1998. Rather than responding to reports of control problems, the aim was to sample rat populations in areas of England and Wales not extensively sampled in the past. Because previous results indicated that anticoagulant-resistant rats were found most frequently on pig or poultry farms, the authors preferentially selected those types of farms for sampling.

Early results from 1995 showed that warfarin-resistant rats were present on one farm in south-west England, and on one farm in the east. The small number of rats trapped on these two farms (two and three, respectively) indicated that the populations were small, and that there were not serious control problems. Testing for resistance to second-generation anticoagulants has not been completed.

The results of a survey between 1995 and 1998 will provide further insight into the distribution and significance of anticoagulant resistance in the U.K.

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