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Anticoagulant resistance in wild Norway rats in New York

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SUMMARY

Wild Norway rats (*Rattus norvegicus*) from several habitats were tested for their susceptibility and resistance to warfarin. Animals were fed 0·005% warfarin in ground oatmeal for periods varying from 1 to 12 days. Rats having no prior exposure to anticoagulants were shown to be susceptible, none having survived a 6-day feeding period. Resistant rats were found on two farms where anticoagulant materials had been used intensively for about 20 years.

INTRODUCTION

The anticoagulant materials proved so effective as rodenticides after their introduction in 1950 that they quickly supplanted acute rodenticides as the main materials used in the chemical control of rodents. Today, it is estimated that anticoagulants represent 95% of the United States' rodenticide market (Mampe, 1969). The world market, likewise, is thought to roughly parallel that of the United States.

The continued rodenticidal effectiveness of the anticoagulant materials has been questioned in the light of rodent resistance to them in the United Kingdom, Denmark and the United States. The first inkling of the problem came from Scotland (Boyle, 1960), where a population of *Rattus norvegicus* on a farm showed a remarkable tolerance to both warfarin and diphacinone. Additional cases of resistance in Norway rats have been uncovered in this same area of Scotland (Boyle, 1967). Meanwhile, Lund (1964) reported the discovery of anticoagulant-resistant Norway rats in the Jutland area of Denmark. Drummond & Bentley (1967) documented other anticoagulant-resistant rat populations in England and Wales and showed the tendency of resistant populations to expand radially. Ophof & Langeveld (1969) reported upon warfarin-resistant rat populations in the Netherlands and upon their subsequent extermination with the use of fluoroacetamide. The first finding of anticoagulant resistance in the United States came from Norway rats living on farms near Raleigh, North Carolina (Jackson, Spear & Wright, 1971; Jackson & Kaukeinen, 1972). The cumulative evidence suggests that wherever anticoagulants are intensively used against relatively large but persistent rat populations, resistance may be developed.

There are indications, then, that resistance may be more widespread in rat populations throughout the world than is generally recognized. Unfortunately, prompt recognition and verification of resistant populations is difficult and, until

an active effort is applied to detect resistance, the full extent of the problem will remain undisclosed.

Laboratory screening tests for anticoagulant resistance have been described (Drummond, 1966; Drummond & Wilson, 1968; WHO, 1970) and yield results that can be replicated with fair accuracy and provide comparisons with results of other workers. Using such procedures, we initiated a study of the anticoagulant susceptibility and resistance of wild Norway rats from several habitats and areas in New York.

MATERIALS AND METHODS

Wild Norway rats were captured alive in cage-traps and returned to the laboratory. They were lightly anaesthetized with carbon dioxide, weighed, measured, sexed, and caged individually. A basal diet of laboratory meal was provided. Sick, pregnant and immature animals were set aside.

After an acclimation period of 3 weeks, rats were provided with a pre-test baiting of ground oatmeal for several days until feeding was stabilized. The amount eaten daily was then measured for 2 days preceding the trial. Then, for periods ranging from 1 to 12 days, groups of rats were allowed unrestricted feeding upon ground oatmeal containing 0·005 % warfarin. The warfarin used was supplied by the Wisconsin Alumni Research Foundation and was found to be a very palatable material (Bowerman & Brooks, 1972). During and following the warfarin offering, animals were observed daily for 14 days from the start of the test for mortality, bleeding and other signs of poisoning. Dead animals were autopsied to verify anticoagulant effects. After the poisoning trial, animals were placed on a basal diet of laboratory meal. Animals were weighed immediately before the warfarin baiting and a terminal weight was obtained. The quantity of warfarin consumed was computed using the initial body weight. Animals weighing less than 150 g. were not used.

RESULTS

Susceptible rats

The purpose of the WHO testing procedure (WHO, 1970) is to measure the susceptibility of rodent populations to a given anticoagulant rodenticide. In order to detect resistant strains of rats, the normal susceptibility of populations having no known prior exposure to anticoagulants must first be established. This is then used as a measure against which suspect resistant populations are compared.

The results given in Table 1 indicate the susceptibility of two populations of Norway rats from refuse disposal sites having no known anticoagulant exposure. The population from Merrick landfill on Long Island resemble very closely data given by Drummond & Wilson (1968) for susceptible rats in England, where all rats died from 3 days exposure to 0·005 % warfarin in ground oatmeal. The second group, from Berlin Township landfill in eastern New York, survived longer feeding periods, but when the relationship between mortality and duration of feeding upon warfarin is examined (Litchfield & Wilcoxon, 1949) it indicates that

Table 1. *Mortality to warfarin-naïve wild Norway rats from several populations after unrestricted feeding on oatmeal bait containing 0·005 % warfarin for various numbers of days*

		Males					Females				
				Mean dose warfarin consumed (mg./kg.)					Mean dose warfarin consumed (mg./kg.)		
Animal source	No. of days feeding	Mean weight (g.)	Mortality	Survived	Died	Mean days to death	Mean weight (g).	Mortality	Survived	Died	Mean days to death
Merrick Landfill	1	372·3	4/12	1·9	2·2	6·8	236·6	1/11	2·4	1·5	8·0
	2	353·2	19/22	3·8	4·6	6·3	244·2	5/10	3·4	4·4	8·0
	3	261·6	10/10	—	7·4	5·5	282·9	10/10	—	7·0	8·3
Berlin disposal site	2	239·0	1/10	7·2	7·8	5·0	174·4	1/7	7·9	8·1	8·0
	3	372·4	9/10	6·7	6·5	6·8	273·5	7/8	3·3	6·1	7·3
	4	324·0	10/10	—	7·3	5·5	252·4	10/14	7·2	5·9	7·1
	5	290·2	5/5	—	12·7	5·6	248·3	9/9	—	10·3	6·7

Table 2. *Mortality to wild Norway rats from several populations after unrestricted feeding on oatmeal bait containing 0·005 % warfarin for various numbers of days*

		Males					Females				
				Mean dose warfarin consumed (mg./kg.)					Mean dose warfarin consumed (mg./kg.)		
Animal source	No. of days feeding	Mean weight (g.)	Mortality	Survived	Died	Mean days to death	Mean weight (g.)	Mortality	Survived	Died	Mean days to death
Wyoming disposal site	6	308·3	10/10	—	7·4	6·4	216·9	7/9	11·6	10·2	7·0
	8	226·5	10/10	—	11·0	6·4	193·4	7/7	—	12·4	6·4
	10	210·4	8/8	—	12·0	6·3	204·9	8/8	—	11·8	6·8
Pittstown, disposal site (moderate poisoning pressure in recent past)	2	256·1	3/10	5·1	4·8	10·3	160·4	3/12	5·8	4·6	8·7
	3	255·1	9/15	6·6	7·4	7·2	161·2	5/12	7·5	9·0	8·8
	4	309·3	9/10	7·1	9·0	6·8	205·3	9/11	14·0	10·3	7·8
	5	328·1	11/11	—	8·6	6·3	194·9	9/10	13·6	12·4	7·2
	6	314·7	9/9	—	7·2	5·4	182·5	10/11	18·5	14·3	7·5
	7	—	—	—	—	—	228·6	14/14	—	14·3	6·7
Selkirk, chicken farm	6	280·2	12/12	—	10·8	6·1	186·1	24/27	12·1	14·1	7·5
Cambridge											
Farm A	6	179·0	2/3	16·4	13·5	9·0	188·8	5/5	—	14·4	7·8
Farm B	6	200·2	4/4	—	14·8	6·5	196·6	6/7	8·9	14·6	7·2
Turkey farm (long-term poisoning)	4	245·2	1/8	9·7	9·3	5·0	179·0	1/8	8·0	6·9	7·0
	6	274·9	6/8	9·2	8·4	6·5	211·7	5/8	9·2	11·9	7·2
	8	296·6	8/8	—	10·8	6·5	186·2	6/8	15·5	14·1	7·5
	10	307·3	12/12	—	10·6	7·3	186·7	10/12	23·5	16·1	7·8
	12	—	—	—	—	—	193·6	9/10	22·1	13·1	8·1

a 6-day feeding on 0·005% warfarin should give a 98% mortality with 95% confidence limits for both sexes. Both populations, then, confirm the usefulness of a 6-day feeding period as a screen for detecting resistant-suspect animals.

There is a clear difference in response of the sexes to warfarin. Females from both populations took significantly longer to die than did males. The mean day of death at Merrick to obtain a 100% mortality for males and females was $5{\cdot}5 \pm 0{\cdot}4$ and $8{\cdot}3 \pm 0{\cdot}6$ ($P = 0{\cdot}01$). At Berlin the respective means were $5{\cdot}5 \pm 0{\cdot}4$ and $6{\cdot}7 \pm 0{\cdot}4$ days ($P = < 0{\cdot}005$).

Resistant and resistant-suspect animals

Bentley (1969) has defined resistant rats in the United Kingdom as those that survived a standard feeding period of 6 days on 0·005% warfarin in the laboratory. Rats that meet this criterion have been found at two areas in eastern New York (Table 2). The first discovered of these populations was found on a turkey farm near Cambridge, New York. Some 80 rats were trapped from this farm over a 1-month period and returned to the laboratory for testing. The turkey farm from which the rats were collected had been poisoned with anticoagulants annually for the past 20 years. The general rural area was characterized by mixed agricultural operations, mainly animal production, such as turkeys, chickens, swine, beef cattle and dairies. Food crops, primarily corn, are grown on some acreages. Rats occurred on several nearby farms; on one of these (farm A) a male rat survived the largest dose thus far taken by a male. This farm, on which swine are raised, lies immediately adjacent to the turkey farm. The other farm (B) is 2 km. to the north-west and is a dairy. The one surviving female here was not considered exceptional.

The second site was a small chicken farm near Selkirk, New York. Some 40 animals were captured here during a month of trapping. This farm had a history of irregular poisonings with anticoagulants whenever the rat population reached intolerable levels. The dosages survived here indicate a very early development in resistance.

The feeding pattern described by Lund (1969), where the amount of food consumed by resistant rats on days 5 and 6 of the test was no less than 75% of that consumed on days 1 and 2, was not seen in any of the rats from the Cambridge or Selkirk areas. Instead, especially on the longer feeding periods, surviving rats interspersed feeding periods of 3–4 days with fasting periods of 2–3 days. This feeding pattern was observed in Norway rats by Drummond & Wilson (1968), who considered it perhaps of practical importance in the poisoning of wild populations.

Rats survived 6-day feeding tests from two other sites but these are considered as resistant-suspect populations only. At Pittstown, females survived doses at 4-, 5- and 6-day feeding periods that suggest emerging resistance. This site had been poisoned moderately with anticoagulants for a period of several years before the animals were tested. At Wyoming village two females survived the 6-day test but all died at 8- and 10-day offerings, so the population is regarded as unexceptional.

Table 3. *Daily intake of warfarin by wild Norway rats when allowed unrestricted feeding upon ground oatmeal containing* 0·005 % *warfarin*

Days of feeding	No. of animals	Mean intake of warfarin (mg./kg.)	Mean daily intake warfarin (mg./kg.)
1	23	2·2	2·2
2	71	5·4	2·7
3	65	7·1	2·4
4	61	8·4	2·1
5	35	10·7	2·1
6	113	11·7	1·9
7	14	14·3	2·0
8	33	12·8	1·6
10	40	13·1	1·3
Totals and means	455	9·3	1·9

DISCUSSION

Drummond & Wilson (1968) proposed the use of warfarin at 0·005 % in baits for susceptibility testing, using a 6-day feeding period as a screening test. Since that time only two papers have appeared using the proposed technique and, consequently, there is very little comparative data. Krishnamurthy, Uniyal & Pingale (1968) carried out susceptibility studies of *Rattus rattus* in Hapur, India, using 0·025 % warfarin in semolina. The roof rat, being considerably more tolerant of warfarin than *Rattus norvegicus*, required a 13-day feeding period for 100 % mortality. These results compare favourably with those obtained by Bentley & Larthe (1959) using the same warfarin concentration against *R. rattus*.

Telle (1971, 1972) reported the results of susceptibility studies in Norway rats in northern Germany. His results are remarkable in that the consumption of warfarin in mg./kg. of rat is quite low. Our observations indicate that an animal feeding upon ground oatmeal bait containing 0·005 % warfarin has a daily intake of anticoagulant ranging from 1 to 4 mg./kg. We found a mean daily intake of warfarin in 455 tested rats to be 1·9 mg./kg. (Table 3). During the course of a 6-day test, total dosage intake by individual animals ranged from 5·0 to 18·5 mg./kg. Drummond & Wilson (1968) present data indicating that their rats have an even larger warfarin consumption daily. Resistant rats are ascribed to populations on the Island of Norderney by Telle. This conclusion is not justified in the light of comparative data from the United Kingdom or the United States.

Our observations upon the occurrence of warfarin-resistant rat populations in New York have led us to believe that resistance may arise in any sizeable persistent rat population that is repeatedly exposed to anticoagulant treatments over a period of years or several decades. Animal operations, at least in this part of the north-eastern United States, seem to offer the best potential for the resistance phenomenon to develop. Additional sites and populations fitting the above description are being sought and studied.

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