Bull. Org. mond. Santé } 1972, **47**, 611-618
Bull. Wld Hlth Org. }

Rodent resistance to the anticoagulant rodenticides, with particular reference to Denmark

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Inherited resistance to anticoagulant rodenticides was discovered in populations of Rattus norvegicus *about 14 years ago. Similar resistance has now been reported from several countries in north-western Europe and from the USA. In order to detect resistance and to control it effectively, basic data on the susceptibility of rat populations are required for each country, and trapping surveys should be made in any area where resistance is suspected. Acute poisons are needed to control resistant rats although the shift from anticoagulants to acute poisons is a retrograde step as far as efficiency is concerned, and increases the hazard of control operations to man and other animals. Resistance to anticoagulants in* Mus musculus *has been reported from England, and resistant mice are probably to be found in other countries also in view of the great individual variation in susceptibility of this species to these rodenticides.*

Apart from a single case of apparent resistance to endrin in a wild population of *Pitymys pinetorum* (pine mouse) after treatment for 11 years (Webb & Horsfall, 1967, only two species of rodent—*Rattus norvegicus* and *Mus musculus*—are reported to have developed an inherited resistance to rodenticides. These two species, however, are not only responsible for great economic losses but also represent a serious potential threat to public health in many parts of the world.

From about 1950 a " golden era " of rat control, based on the use of anticoagulant rodenticides, was experienced in many countries, particularly in Western Europe, where it lasted for almost 10 years. During this period the anticoagulants—first dicoumarol and its derivatives, especially warfarin, and later the indandiones also—more or less replaced the " acute " poisons and led to decreases in the level of rat infestation in many countries. Control operators soon came to realize that rats could virtually be exterminated over large areas; at the same time, however, prebaiting and other techniques previously used were practically forgotten.

The marked difference between the success rates for the acute poisons and the anticoagulants depends on the following factors. All anticoagulant rodenticides compete with vitamin K in the body for the synthesis of a protein involved in the complex clotting mechanism of the blood. When the anticoagulant replaces vitamin K this protein is rendered inactive, and gradually the clotting capacity of the blood decreases, until fatal spontaneous internal bleeding occurs. Since this process is rather slow the rats normally feed for 2–4 days before warning symptoms occur, and by that time the lethal dose has usually been exceeded.

The effect of the non-anticoagulant poisons is generally much more acute, and the rats often experience symptoms of poisoning a few minutes after ingesting the bait. Brown or Norway rats (*R. norvegicus*) are very suspicious of unfamiliar baits and are likely to eat only a sublethal dose. After having recovered, the rats cannot readily be induced to feed again on the same bait for a considerable time.

As the anticoagulants are cumulative in their effect, the concentration in the bait can be very low, e.g., 0.005–0.05%, and the baits are therefore more readily accepted by the rats. On account of the chronic effects of these poisons, the risks to man and most domestic animals are rather small. Furthermore, as vitamin K is an effective antidote and since secondary poisoning is very unlikely to occur, the anticoagulants can be considered to be almost ideal rodenticides.

In large-scale operations prebaiting with unpoisoned bait, which as a rule is necessary in order to induce the rats to consume a lethal dose of an acute poison, is very laborious and expensive. The introduction of the readily accepted anticoagulant rodenticides saved both time and money without the risk of inducing

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bait-shy behaviour in the rats. Attempts to create " rat-free " areas and towns, based primarily on permanent baitboxes containing anticoagulants, now seem to be successful in England, the Federal Republic of Germany, and Denmark, although at one time they would have seemed utopian.

Thus, the detection in 1958 of rat populations in Scotland that were resistant to warfarin (Boyle, 1960) followed by similar discoveries in Wales in 1960 (Drummond, 1966), Denmark in 1962 (Lund, 1964), the Netherlands in 1966 (Ophof & Langeveld, 1969), the Federal Republic of Germany in the period 1968–71 (H. J. Telle, unpublished report to WHO, 1971), and the USA in 1972 (Jackson & Kaukainen, 1972; Brothers, 1972; Brooks, personal communication, 1972) were not merely reports of resistance to a rodenticide, but represented a threat to rat control in those countries.

DETECTION OF WARFARIN RESISTANCE

Apart from the Netherlands, where the authorities were on the alert after receiving reports from the United Kingdom and Denmark, the discovery of resistance to anticoagulants followed the same course in all the countries concerned. Up to the time when resistance was detected no regular and systematic trapping of rat populations had been carried out to check the effectiveness of the anticoagulants and to obtain basic data for estimating the susceptibility of rats to these compounds. Complaints about failures of control operations were from time to time received by the local authorities, but when the complaints were closely investigated, they were always found to be due to faulty techniques, the poor quality of the bait, or the availability to the rats of food containing extraordinary amounts of vitamin K. This was also the view taken when cases of resistance were reported by local operators. In Denmark, for example, it was claimed in 1962 that on a few farms in eastern Jutland, rats could not be killed with warfarin, and precious time was wasted before rats were trapped on those farms and tested in the laboratory. It was then established that a certain degree of tolerance had developed; two-thirds of the rats survived a routine test with 1 g of bait containing 0.025% warfarin for 5 successive days. The consequences, however, were not realized until further tests revealed that a considerable proportion of the rats were able to survive for months on 0.05% warfarin bait as the only food; some pregnant females even gave birth to live young during this period.

SCREENING TESTS

Until 1966 trapped rats from the area of resistance and suspected areas of resistance in Denmark were tested by feeding them on 0.05% warfarin bait for 10 days; those surviving were termed " resistant ". On the basis of this definition, a clear separation of susceptible and resistant individuals was obtained, with very few intermediates. At a conference of the European and Mediterranean Plant Protection Organization (1967) a standard test was proposed for identifying warfarin-resistant individuals of *R. norvegicus*, based on investigations carried out by Drummond & Bentley (1967). According to this test a brown rat is resistant if it survives for 6 days on a diet of 0.025% warfarin bait. A more elaborate procedure for measuring the susceptibility level of a particular rodent species to a given anticoagulant has been suggested by Drummond (unpublished report to WHO, 1966).

The standard screening test for resistance in rats was soon adopted in Denmark, and in the following years it was shown that various degrees of resistance could be found in the rat populations concerned (Lund, 1969). While some rats from the area of resistance continued to feed at the same level throughout the test period and survived with no signs of poisoning, others stopped feeding on days 5 or 6 and were often characterized by pale feet and small external haemorrhages. However, the latter animals recovered and survived for months. A third group of rats fed at the same level during the whole period of the test died from internal bleeding a few days later. The typical feeding behaviour of " normal " susceptible rats from other areas is a marked decrease in, or a complete cessation of, the consumption of bait on the fifth or sixth day at the latest, and death generally occurs 3–10 days after the start of the test.

In the United Kingdom similar differences are found between Scottish and Welsh rats, and between rats from different areas of resistance in England (Drummond & Wilson, 1968).

A rapid method of distinguishing between resistant and susceptible rats is used in the United Kingdom (Greaves & Ayres, 1967). A single dose of 1 mg of warfarin per kg of body weight is injected in rats, and blood samples for prothrombin time estimations are taken immediately before, and 24 hours after, the injection. A good correlation is generally found between the results of this test and those of the standard feeding test. Resistant rats that survive the feeding test show little or no change in the prothrombin time,

whereas rats that die as a result of the feeding test show a marked change.

AREAS OF RESISTANCE

The conditions under which resistant rat populations have arisen are similar in all the countries concerned. The areas are typically rural with small villages and scattered, often old, farm buildings with poor sanitary conditions that cannot be made ratproof. Very often large rat populations are found in deep-litter poultry houses and in old barns with ready access to grain stores, silage, chicken food, and garbage in piggeries. In the United Kingdom, cornricks situated near barns often provide good shelter and food for rats.

The first reported case of resistance to anticoagulants in rats was established on a farm near Glasgow, Scotland, but since about 90% of the rats trapped on this farm were resistant, and since other resistant populations were detected up to 20 km away during the next 2 years, its seems unlikely that resistance originated on the farm. In 1962 the known area of resistance was about 24×8 km and comprised 7 different sites, but no systematic trapping could be carried out and the true extent of the area is unknown. Resistant rat populations are now found in a fairly extensive region between Edinburgh and Glasgow. It seems obvious that some spreading has occurred, but it has certainly not exceeded 5–10 km in the past 5 years (Boyle, personal communication).

The second area of resistance to be detected is situated on the border between Wales and England in the Welsh county of Montgomeryshire, where two adjacent farms were found to have resistant rats in 1960. After the original infestation had been treated no new cases were reported in the area for about a year, but several new sites then appeared and the number increased during the following years, the area expanding into the English county of Shropshire at a rate of about 4.6 km radially per year (Drummond & Bentley, 1967). This rate of spread is similar to that of a rat population in unoccupied land (Drummond, 1970).

At about the same time two areas in England in the counties of Somerset and Nottinghamshire seem to have had resistant rat populations; they were, however, successfully controlled with acute poisons before the resistance was fully confirmed. These areas differ from all other known areas in that they are not rural, one being a city block and the other a municipal refuse tip. In 1966 rats caught on two farms in Gloucestershire and four in Nottinghamshire showed resistance, but the difference between susceptible and resistant individuals was not as marked as in those from the Scottish and Welsh populations. It was suggested by Drummond (1970) that resistance in populations from various sites in England may be of different types. The resistant rats from Gloucestershire and Nottinghamshire seem in any case to have been completely exterminated. A larger area of resistance was found in Kent in 1968, but it has not been examined in detail (Greaves, 1971). Since 1969 a few more cases have occurred in Carmarthenshire, Suffolk, and Berkshire, but apparently they are unconnected with the cases reported earlier (Drummond, personal communication).

Outside the United Kingdom the first area of resistance to be reported was on the peninsula between Vejle and Horsens in Jutland, Denmark. When it was detected in 1962 five or six old farms, close to each other, were involved, but, as trapping later indicated, it seems likely that resistance had by that time already spread to a larger area, making countermeasures almost hopeless. In the spring of 1972 the presence of resistant rats was confirmed in more than 60 sites on the peninsula, and trapping has revealed cases of resistance in 15 municipalities, some of them up to 80 km from the original sites. The total area involved now covers roughly 9 000 km^2. All the same, it seems likely that resistance has not arisen independently in the various new sites; this assumption is based on the observations that rats trapped in the " new " areas included a much lower proportion of resistant individuals than did those trapped on the peninsula, and that rats from the " new " sites showed a lower level of resistance.

The next area outside the United Kingdom where resistance in the brown rat was proved by laboratory investigations, was the Province of Drenthe in the north-eastern part of the Netherlands (Ophof & Langeveld, 1969). Two populations tested in 1966 showed some degree of resistance. They were immediately controlled by means of an acute poison (fluoroacetamide), and apparently the operations were successful since no new cases have so far been found in the Netherlands.

During the period 1968–71 rats trapped in different sites in Lower Saxony, Federal Republic of Germany, were tested for resistance (H. J. Telle, unpublished report to WHO, 1971). The preliminary results indicate that various degrees of resistance are present in rats on the islands of Norderney and Borkum, as well as in the cities of Oldenburg and Nordhorn.

Recent reports from the USA (Jackson & Kaukainen, 1972; Brothers, 1972; Brooks, personal communication, 1972) reveal that, as had been expected for several years, resistance has become established in American rat populations. In North Carolina 25 rats trapped on farms near Raleigh in 1972 were all resistant and survived the 6-day standard test. This high level of resistance may indicate that the mutation had been present in the rat populations for several years before it was detected.

A national survey to determine whether resistance may exist undetected was undertaken in 30 cities in the USA in the spring of 1972. The first report from the New York State Department of Health shows that that 1 of 17 rats from Newark, N.J., and 1 of 35 rats from Norfolk, Va., survived the screening test. These figures are quite similar to those found in " new " areas of resistance in Denmark, and seem to represent an early stage of resistance.

LABORATORY INVESTIGATIONS ON RESISTANCE

Genetics

It was soon established in the United Kingdom as well as in Denmark that resistance to anticoagulants in rats is an inheritable character, and crosses of resistant rats from Wales with a domesticated albino strain showed that resistance, at any rate in this area, is due to a single dominant autosomal gene (Greaves & Ayres, 1967). The assumption of a single gene mechanism is based not only on back-crosses of survivors from the 6-day test to the susceptible albino strain for 5 generations, but also on the finding of a genetic linkage between coat colour and resistance (Greaves & Ayres, 1969a). This mapping of the resistance gene is of particular interest when the kind of resistance occurring in other areas, and possible differences, are to be evaluated.

The genetic nature of resistance was also studied in the USA on Welsh resistant rats and their descendants (Pool et al., 1968), the English findings being confirmed. Hermodson et al. (1969) crossed heterozygous Welsh rats with a susceptible albino strain and obtained a ratio of 0.93 : 1 in the offspring, which is very close to the 1 : 1 ratio expected. From a few rats producing only resistant offspring in backcrosses, Hermodson et al. developed a homozygous strain resistant to warfarin.

It seems likely that a single dominant gene is also responsible for anticoagulant resistance in the Scottish rats (D. A. Price-Evans & P. M. Sheppard, unpublished report to WHO, 1966), but the difference in the level of resistance in the Welsh and Scottish populations may indicate that the genes are not identical. The results obtained from genetic crosses of resistant rats in Denmark do not fit the theory that a single dominant gene is responsible for the resistance. A marked difference was found in the offspring of resistant male and female rats crossed with susceptible wild rats (23.3% and 42.6% of the offspring resistant, respectively). After 4 generations, not more than about 50% of the offspring from resistant parents were resistant, compared with 44% in the first generation. Recently, however, the offspring of a Danish resistant male crossed with a female from the English susceptible strain have been tested for resistance and the results are very similar to those obtained with Welsh rats (Greaves, personal communication).

The effect of other anticoagulants

When resistance to warfarin was detected in the United Kingdom and Denmark, other anticoagulant rodenticides were examined in the hope of finding a substitute. So far, coumachlor, dicoumarol, diphacinone, chlorophacinone, phenylindanione, and pindone have been tested and resistance has been found to all of them, including the distantly related indandiones, which had never been used in Denmark up to that time.

In 1967, however, coumatetralyl, which is closely related to warfarin, turned out to be more effective than the other anticoagulants against resistant rats in Scotland and Wales (Great Britain, Ministry of Agriculture, Fisheries, and Food, 1968), and preliminary tests in Denmark produced similar results.

It was soon established, however, that some degree of resistance to coumatetralyl was also present in some warfarin-resistant rat populations in the United Kingdom (Greaves & Ayres, 1969b) and in Denmark (Lund, 1969). Since a large proportion of the warfarin-resistant rats were killed in the field by coumatetralyl, and since a rat has never been known to survive a prolonged feeding test of 14 days, this compound is still used in areas of resistance. The feeding behaviour of rats offered coumatetralyl bait may help them to survive, since they tend to feed irregularly and intermittently; such feeding behaviour is very seldom seen in Danish tests when warfarin is used (Lund, 1969).

Other laboratory investigations on resistance

Resistance to anticoagulants was at first thought to be the result of an increased ability of the rats to

utilize vitamin K in the food; mineral oil was therefore added to the warfarin bait in order to reduce the absorption of vitamin K. This procedure had only a slight effect on Scottish and Danish rats but caused a high rate of mortality among resistant Welsh rats in the laboratory. As the mineral oil seems to affect only the uptake of vitamin K from the bait and not that from other sources, the advantage of the method with resistant rats in the field is negligible. The addition of antibacterial agents such as sulfaquinoxaline to the bait in order to reduce the amount of vitamin K produced by intestinal bacteria was not more effective. The administration of phenylbutazone in an attempt to prevent a possible binding of warfarin to serum proteins, and of ethionine to inhibit abnormal enzyme activity that might be responsible for the rapid breakdown of warfarin, was also unsuccessful.

No significant difference has been found in the response of resistant rats to injected and oral doses of warfarin; it therefore seems unlikely that the resistance is due to the rapid excretion of warfarin or to its conversion to a nontoxic substance (Price-Evans & Sheppard, unpublished data, 1966).

Investigations carried out in the USA on descendants of resistant Welsh rats (Hermodson et al., 1969) have thrown much light on the mechanism of resistance. Studies with ^{14}C-warfarin showed no difference in the rate and manner of warfarin metabolism in normal and resistant rats. On the other hand, vitamin-K-depleted resistant rats fed for 3 days on a diet low in vitamin K, and thereafter fed a measured dose of vitamin K_3, required much larger amounts of the vitamin to restore the prothrombin level of the blood than did normal rats. Moreover, while heterozygous resistant rats required about twice as much vitamin K_3 as susceptible rats, homozygous rats needed 20 times as much as normal rats.

THE MECHANISM OF RESISTANCE

The results obtained by Hermodson et al. (1969) are explained by those authors on the basis of a rather simple hypothesis. It is assumed that vitamin K and the anticoagulants compete for a site on a protein necessary for the synthesis of vitamin-K-dependent clotting factors. A mutation in the resistant rat may have lowered to some degree the affinity of that site for vitamin K, and at the same time lowered its affinity for anticoagulants to a much greater extent. Resistance in the Welsh rats is claimed to be dominant since heterozygous and homozygous rats both have a supply of the altered protein, which is relatively unaffected by high levels of warfarin. The homozygous rats, however, having only the altered protein with a lowered affinity for vitamin K, have much higher requirements for the vitamin.

This theory is supported by the discovery of the protein concerned in the ribosomes in the liver cells (Hermodson et al., 1969). Using ^{14}C-warfarin, Hermodson et al. (*op. cit.*) showed that the ribosomes from normal rats were able to bind 2 or 3 times as much warfarin as were those from resistant rats.

Some other phenomena previously encountered in the United Kingdom and Denmark are also explained by the hypothesis. Rats from the areas of resistance, or offspring of crosses of these rats, may die suddenly with internal bleedings, although they have never, or not for several months, been exposed to an anticoagulant. This phenomenon can readily be explained by the theory of decreased ability to utilize vitamin K in the food. Vitamin K deficiency may also be responsible for a decrease in the proportion of resistant individuals in a mixed population of rats kept for 3 years in an outdoor pen (Lund, 1968). This may indicate that resistance would disappear if the effect of the mutation were not counteracted by selection with anticoagulants.

COUNTERMEASURES

Resistant rats seem to have been completely eradicated in the Netherlands by the immediate application of acute poisons, and the sites in England where resistance seems to have been controlled were characterized by an early stage in the development of resistance. It appears, therefore, that resistant rat populations should be discovered as early as possible if there is to be any hope of eliminating them. In the three original areas in Scotland, England, and Denmark, the reaction may have been too slow, the necessary financial and labour resources may not have been available, or the area of resistance may have been too large for effective control measures to be applied by the time the resistance was discovered.

Between the years 1962 and 1965 an attempt was made to estimate the area of anticoagulant resistance in Scotland and to eliminate the rat population in a small part of the area (4×3 km, by means of warfarin followed up with acute poisons (C. M. Boyle & J. H. Cuthbert, unpublished report to WHO, 1966). In spite of the efforts that were made, complete clearance was not obtained. Similar results were obtained in another trial and it was concluded that even if the

spread of resistance could be considerably retarded, there was always the possibility that a few resistant rats would survive even the most intensive treatment with acute poisons. Coumatetralyl has now replaced warfarin and apparently very few practical difficulties with resistance to this compound have been encountered in the field. Recent reports seem to indicate that the level of rat infestation is now considerably lower than it was in 1965 (Boyle, personal communication). This may be partly the result of using coumatetralyl, but partly also the result of improvements in environmental standards and of a general awareness by the public of resistance in rats.

In the Montgomeryshire/Shropshire area of England and Wales resistance was investigated from 1962 by means of trapping surveys, and in 1966 a containment zone 5 km wide was established around the outer limits of the known area. Within this zone only acute poisons (mostly zinc phosphide) were to be used. It was hoped in this way to stop the emigration of resistant rats to other parts of the country. After the containment zone had been enlarged to include a pocket of resistance a few km to the south-east, it surrounded an area of about 3 100 km^2. Even if the spread of resistance was delayed to some extent, by 1971 it was clear that resistant rats had spread through and beyond the containment zone and the work was therefore discontinued (Drummond, 1971).

In Denmark, the situation is similar to that in Scotland. It had been hoped to prevent the resistant rats from spreading outside the peninsula where resistance originated by establishing a dilution zone on the western side of the peninsula with permanent stations containing bait poisoned with thallium sulfate. Before this could be arranged financially, however, trapping revealed cases of resistance several km beyond the absolute limit for the proposed control zone. As in the United Kingdom, coumatetralyl was substituted for warfarin in the area of known resistance and in sites suspected to contain resistant rats. This treatment was followed up with thallium sulfate and zinc phosphide poison-baiting whenever resistance to coumatetralyl was encountered.

Unfortunately, the level of rat infestation on the peninsula does not seem to be much lower than it is in other parts of the country, in spite of the great efforts made by the control operators in the area. The spread of resistance has certainly not been greatly delayed, and it is expected that resistance to anticoagulants will be a problem in most parts of Jutland in the next few years. Since October 1972 the use of warfarin for rat control has been prohibited in Jutland, coumatetralyl being the only anticoagulant permitted, even in areas where resistance has not yet been found.

It is remarkable that so few of the countries where anticoagulants have been used continuously for rat control for more than 15 years have reported cases of resistance—possibly owing to a failure to detect resistant rat populations (since no country carries out systematic trapping in suspected areas) or because other rodenticides are used at once if the effect of anticoagulants is unsatisfactory in some areas. It is not surprising therefore that resistant rat populations were detected in the Federal Republic of Germany and the USA as soon as surveys were made. Much can be learned by other countries from the Netherlands of the importance of early detection, and from experience in the United Kingdom, Denmark, the Federal Republic of Germany, and the USA of the disastrous effect of late discovery and hesitating acceptance of the fact of resistance. However, resistance is not easily discovered if basic data on susceptibility levels of rats to anticoagulants are not available for each country and if resistance in rat populations is not periodically checked against these data.

RESISTANCE IN THE HOUSEMOUSE

The susceptibility of normal brown rats to anticoagulants does not vary much but there is great individual variation in the response of housemice (*Mus musculus*) to the same compounds. While a 6-day feeding test with 0.025% warfarin bait will produce almost 100% mortality in brown rats, 9–10% of housemice from previously untreated populations may survive a 21-day test with the same concentration of warfarin (Rowe & Redfern, 1964). Obviously, an even larger proportion of mice may survive in the field, where other sources of food are always available.

The use of anticoagulants for the control of housemice in Denmark has been discontinued in favour of acute poisons, particularly crimidine. It is evident that anticoagulant resistance may develop relatively quickly in a species with a wide range of susceptibility, and in the Federal Republic of Germany a certain degree of resistance could be produced in the laboratory by the selection of mice with warfarin in relatively few generations (Roll, 1966). Laboratory investigations in the United Kingdom revealed decreased susceptibility to warfarin in some populations of housemice from urban areas where warfarin had

been used in previous years (Dodsworth, 1961).

More than one gene seems to be involved in anticoagulant resistance in the housemouse (Rowe & Redfern, 1965; Roll, 1966). Laboratory investigations on the vitamin-K-dependent clotting factors have shown that after 1 day on a 0.025% warfarin bait diet the level of these factors in the blood of resistant mice is considerably reduced, but during the following days on the same diet the level returns more or less to normal, indicating that resistance may be partly the result of an inheritable ability to develop tolerance (Rowe & Redfern, 1968). The same investigations showed that some mice were able to live for 3 weeks with practically unclottable blood without any sign of haemorrhages. This suggests a more complex resistance mechanism than in the rat.

An international standard test for detecting resistance to anticoagulants in housemice cannot be proposed on account of the great individual variation in response and the obvious possibility of differences in the susceptibility of geographical races of housemice, as suggested by Roll (1966). Bait-shyness is a minor problem in the housemouse, and this species seems less suspicious of poisons than the brown rat; therefore, acute rodenticides can be used more successfully. Thus, resistance to anticoagulants in the housemouse does not appear to be such a serious problem as resistance in the brown rat.

RÉSUMÉ

RÉSISTANCE DES RONGEURS AUX RODENTICIDES ANTICOAGULANTS, EN PARTICULIER AU DANEMARK

Les rodenticides anticoagulants ont fait preuve d'une efficacité remarquable dans la lutte contre le rat brun (*Rattus norvegicus*) depuis le début des années 1950, et ils ont permis de détruire une grande partie des populations de ce rongeur aux Etats-Unis d'Amérique et dans de nombreux pays d'Europe. Cependant, la résistance du rat brun à la warfarine et à d'autres anticoagulants, décelée en 1958 en Ecosse, en 1960 au Pays de Galles, en 1962 au Danemark, en 1966 aux Pays-Bas, en 1968/71 en République fédérale d'Allemagne et en 1972 aux Etats-Unis, pose de sérieux problèmes.

On considère que le rat brun est résistant lorsqu'il survit après 6 jours d'un régime contenant 0,025% de warfarine. En Ecosse, au Pays de Galles et au Danemark, les tentatives visant à empêcher la dissémination des populations de rats résistants ont échoué; seuls les Pays-Bas ont apparemment réussi à éliminer la résistance en recourant très précocement à l'emploi de poisons à toxicité aiguë comme le fluoroacétamide.

Au Danemark, la présence de rats résistants a été constatée sur un territoire d'environ 9000 km². Il est probable que le caractère s'est répandu à partir des premiers foyers détectés car la résistance se manifeste avec une acuité et une ampleur moindres dans les régions récemment atteintes. En République fédérale d'Allemagne et aux Etats-Unis, des investigations approfondies ont immédiatement montré l'existence de populations de rats résistants à des degrés variables. Dans certains cas, l'intensité du phénomène apporte la preuve de son ancienneté bien qu'il soit resté ignoré pendant des années.

Des recherches sur les aspects génétiques de la résistance aux anticoagulants ont été faites sur des rats du Royaume-Uni et du Danemark. Chez les premiers, la résistance semble dépendre d'un gène unique dominant, mais les données obtenues chez les seconds lors d'épreuves de croisement n'ont pas confirmé le fait.

En dehors de la résistance, la seule différence physiologique entre les rats résistants et les rats sensibles est que les premiers ont besoin d'un apport beaucoup plus élevé de vitamine K (deux fois plus élevé pour les rats résistants hétérozygotes; vingt fois plus élevé pour les homozygotes). Dans certains cas, les rats résistants ne peuvent survivre que dans un milieu où la vitamine K est particulièrement abondante.

La résistance s'exerce à l'égard de tous les autres anticoagulants, y compris les indandiones. Cependant, le coumatétralyl fait preuve d'une efficacité supérieure contre les rats résistants; c'est actuellement le seul anticoagulant utilisé dans la plus grande partie du territoire danois (Jutland).

Chez la souris domestique (*Mus musculus*), les variations individuelles de la sensibilité à la warfarine sont beaucoup plus marquées que chez le rat brun et le risque d'apparition rapide d'une résistance aux anticoagulants est plus grand. Des populations résistantes ont été signalées au Royaume-Uni. Il semble que le caractère soit transmis héréditairement par l'intermédiaire de plusieurs gènes. Chez la souris, les conséquences de la résistance aux anticoagulants sont moins graves que chez le rat, car l'espèce peut être efficacement combattue par les poisons à toxicité aiguë.

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