Chemicals in Rodent Control

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1 Introduction

For centuries rodent pests have deprived man of his food and given disease and death in return. In many areas of the world, this menace has had to be accepted as a part of the environment since rodent control measures were either ineffective or too expensive. Early attempts at disinfestation were often hampered by man's own ignorance of rodent behaviour; however, modern techniques have now evolved so that highly efficient control of rodent pests is often possible.

A number of general accounts[1-4] of the problem and specialized reviews of *e.g.* rodent behaviour with respect to control,[5] rodenticides,*[6-9] repellants,[10-12] chemosterilants,[13-15] *etc.*, are available, but a review devoted solely to the contribution made by chemicals has not appeared hitherto. The objective of this article is to describe the chemical background surrounding the control of rodent pests and to stimulate interest in chemicals, both those in use and those of potential usefulness in rodent control.

* The term rodenticide in this article covers only the chemical poisons that bring about the death of the rodent pest directly, rather than the broad interpretation used elsewhere[16] which includes chemosterilants, repellants, *etc.*

[1] R. A. Davis, 'Control of Rats and Mice', Ministry of Agriculture, Fisheries, and Food Bulletin No. 181, 1967.
[2] A. S. Strivastava, *Labdev. J. Sci. Tech.*, 1966, **4**, 207.
[3] T. J. Gray, *World Health*, 1967, 3.
[4] M. A. C. Hinton, 'Rats and Mice as Enemies of Mankind', British Museum (Natural History), Economic Series No. 8, 1918.
[5] D. Chitty and H. N. Southern, 'Control of Rats & Mice', Clarendon Press, Oxford, 1954, 3 vols.
[6] J. H. Krieger, *Agric. Chem.*, 1952, **7**, 46.
[7] E. Enders, 'Chemie der Pflanzenschutz und Schadlingsbekampfungsmittel', Springer-Verlag, Berlin, 1970, p. 601.
[8] D. H. Frear, 'Chemistry of the Pesticides' ,Van Nostrand, New York, MacMillan, London, 1955, p. 437.
[9] E. M. Mills, *Pest Control*, 1955, **23**, 14.
[10] J. F. Welch, *Agric. Food Chem.*, 1954, **2**, 142.
[11] H. V. Thompson, *Forestry Abstracts*, 1953, **14**, 129.
[12] J. F. Welch, Proceedings of the Third Vertebrate Pest Conference, California, ed. M. Cummings, 1967, p. 36.
[13] J. E. Brooks and A. M. Bowerman, *Soap*, 1969, **45**, 58.
[14] W. E. Howard, 'Pest Control', Academic Press, New York and London; *Biocontrol and Chemosterilants*, 1969, **10**, 343.
[15] R. E. Marsh and W. E. Howard, Proceedings of the Fourth Vertebrate Pest Conference, California, 1970, p. 55.
[16] 'Webster's 7th New Collegiate Dictionary', G. Bell & Sons Ltd., London, 1969, p. 745.

No apology is given for including brief references to non-chemical procedures, since integrated programmes are essential for successful control. Particular reference is made to rodents of the U.K. that are commensal, *i.e.* rodents dependent on man for food and shelter, but examples of procedures used to combat other rodent pests are included.

2 Rodent Pests

One of the largest groups of animals in the animal kingdom in the Class MAMMALIA is the Order RODENTIA, which contains upwards of 3000 species.[17] In the rodent classification (see Table) rats and mice are grouped together in the same family MURIDAE. (Contrary to popular belief, the rabbit is included in the Order LAGOMORPHA and hence it is not strictly a rodent.)

The name rat may be correctly applied to about 500 species of rodent, but only two species (*Rattus norvegicus* and *Rattus rattus*) are of worldwide significance, and both these species appear in Britain. *R. norvegicus* (Berkenhout), (the common rat, brown rat, *etc.*) infests most habitats provided by man and has the capacity to adjust to almost any environmental condition, although it is mainly a burrowing and water-loving animal of the temperate zone. *R. rattus* (Linnaeus), (black rat, ship rat, *etc.*) exists in three subspecies (see Table), which in Britain and some other countries interbreed freely and so are ecologically indistinguishable.[18] *R. rattus* is more of a climbing or arboreal species and is particularly widespread in the tropics. *R. rattus* has been called the plague rat for it was a vector in the plagues of the Middle Ages. It is now rarely observed away from seaports and dockyards in Britain. At least 130 species of mice exist and four types are found in Britain, although it is only the house mouse, *Mus musculus* (*Linnaeus*) that is a common urban pest.

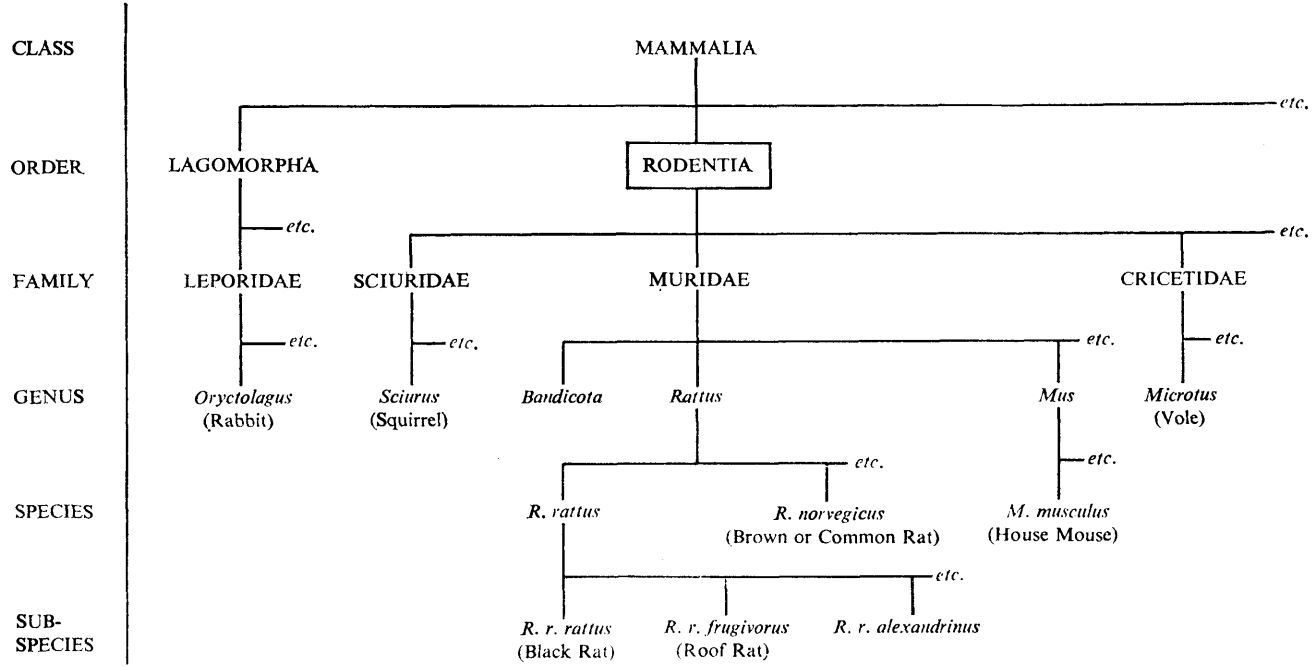
3 Need for Control

A. Damage.—In common with other rodents, the rat has incisor teeth which grow throughout life. The outer enamel of the incisors has a value of 5.5 on the Moh scale of hardness, so that lead pipes, metal-sheathed cables, insulated electrical wirings, plastics, hardwoods, *etc.*, are all open to attack by rodents. It has been estimated[19] that in Britain some fifty million rats exist, causing £50—60 million worth of damage per year.

B. Food Losses.—Food losses due to rodent attack can be severe, the food being taken from the field, granaries, stores, and domestic properties. It has been estimated[3] that the total annual world loss of stored cereals and rice for which rats are responsible exceeds 33 million tons.

[17] J. Z. Young, 'The Life of Vertebrates', Clarendon Press, Oxford, 1964, p. 652.
[18] E. W. Bentley, 'Biological Methods for the Evaluation of Rodenticides', Ministry of Agriculture, Fisheries, and Food, Tech. Bull., No. 8, 1958.
[19] P. L. G. Bateman, 'Rats', Advice and Action Ltd., Public Relations Consultants, East Grinstead, Sussex.

Table *Classification of Rodents**



* Assistance from J. M. Ingles, Mammal Section, British Museum (Natural History), London, S.W.7, is gratefully acknowledged.

C. Disease.—Rats and mice are known to transmit at least thirty-five diseases, and carry many different kinds of lice, fleas, ticks, and mites.[2] One disease known as the plague was responsible for the death of twenty-five million people during the fifteenth century. This disease, which is still found in many parts of the world, is caused by the bacterium *Pasteurella pestis*, and is spread from rats to man by a flea (*Xenopsylla cheopis*). Many other serious diseases are spread by rats and mice, *e.g.* Leptospiral Jaundice (Weil's Disease), 'Rat bite fever' (*Soduku*), and Trichinosis. In control measures it is important to aim for total extermination, as the very existence of rodent pest populations in and around human habitation is a potential health hazard.

4 Control of Rodent Pests

Although shrouded in superstition and folklore, a number of old-fashioned methods were partly effective since they were based, like modern techniques, on careful observation of animal pests and their behaviour. Skilled 'rat-catchers' employed in medieval days knew much about these habits and one such person hired by a German city probably gave rise to the legendary tale of the highly successful Pied Piper of Hamelin.

Present day control tackles the problem from both the offensive and defensive standpoints. Mechanical control is valuable in integrated control procedures and includes the use of traps,[20] barriers, and general rodent-proofing.[5,21] A number of biological control methods are of interest. Introduction of predators to destroy rodent pests was one of the first recorded extermination methods,[3] but incomplete disinfestation and disturbances of the ecological balance restrict their value.[22] An infectious disease pathogenic only to the rodent pest has also been considered. Incorporation of cultures of *Salmonella enteritidis* in rat baits is effective but non-specific. Danger to man and domestic animals[23] has resulted in the cessation of this practice. A specific virus infection, myxomatosis, was more successful in limiting rabbit populations.[24,25] Specific non-pathogenic diseases, which could render animals more susceptible to chemical poisons, may have their place, *e.g.* parasitaemia in the canefield rat (*Holochilus sciureus*) of British Guiana[26] increases its susceptibility to anti-coagulant poisons.

The essential step in any ideal control operation is the elimination of the rodent's two basic living requirements, namely food and shelter.[1] Even if this is not practicable, however, merely the combination of good hygiene, tidy storage, and frequent refuse disposal is a great aid to subsequent extermination work.

Nearly all modern extermination procedures depend on chemical methods.

[20] 'Trapping Rats and Mice', United States Dept. of the Interior Fish & Wildlife Service, Leaflet No. 320, 1961.
[21] 'Controlling Rats & Mice, Fundamentals of Rodent Proofing', United States Dept. of the Interior, Fish and Wildlife Service, Leaflet No. 313, 1961.
[22] Ref. 12, p. 137.
[23] J. Taylor, *Lancet*, 1956, **1**, 630.
[24] H. V. Thompson, *Ann. Appl. Biol.*, 1953, **41**, 358.
[25] F. Fenner, *Brit. Med. Bull.*, 1959, **15**, 240.
[26] J. F. Bates, Proceedings of the 11th Congr. I.S.S.C.T., Mauritius, 1962, p. 695.

The rodenticides are accepted as the main eradication tool, but other chemicals such as chemosterilants are useful in supporting roles.

The main factors that need to be kept in mind when using chemicals are the safety precautions necessary to protect man, his livestock, and other animals. In order to counteract possible outbreaks of resistance, a continual check must be made on rodenticidal performance.

5 Rodenticides

Rodenticides are normally employed in solid baits or in dust (p. 396) or liquid form while suitable volatile chemicals have found use as fumigants (p. 397). Although toxicity (conveniently expressed as the median lethal dose, LD_{50}, in mg/kg, p.o.) is an essential pre-requisite of an effective rodenticide, it is not the only criterion upon which an ideal rodenticide is based. Additional features[6–8] of an ideal rodenticide are set out below:

(i) Toxic action slow, to allow animal to consume a lethal dose.
(ii) The poison should not be unpalatable, and preferably odourless.
(iii) Symptoms of acute poisoning should be absent; no bait shyness.
(iv) The poison should be specific to the species to be controlled.
(v) The manner of death, preferably humane, should not arouse suspicions in surviving animals.
(vi) No difference in susceptibility due to age, sex, or strain should be present.
(vii) There should be no danger of secondary poisoning through animals eating poisoned rodents.
(viii) No immunity or build-up of tolerance to the poison should develop.
(ix) The chemical compound in the bait should be stable under varied environmental conditions.
(x) To allow easy removal of corpses, the animals should preferably die in the open.

Since these requirements are numerous and difficult to achieve in practice, a high toxicity and palatability with one or more safety features is the usual aim. The chemical poison should be of constant composition within a fixed particle size range[18] (previously determined for optimum toxicity) and be easily available in a pure state. The effects of possible impurities which might be present in the large scale preparation of the rodenticide should also be tested on the pest species and other animals. The carcinogenic effects of one impurity sometimes found in the rodenticide antu (α-naphthylthiourea) has led to the removal of this rodenticide from the market in the U.K.[27]

The bait chosen and other additives (p. 398) greatly contribute to the success or otherwise of a particular poison, but as yet a poor rodenticide has not been transformed into a good one by changes in formulation.

From the foregoing it can be seen that the search for potential rodenticides is more difficult and complex than might at first appear. One approach, using

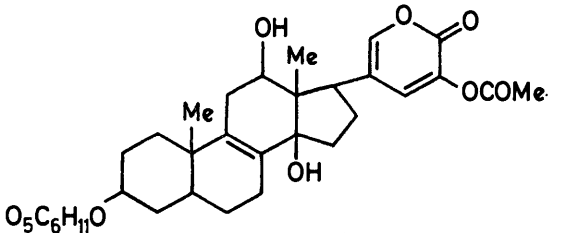
[27] Anon. *Lancet*, 1966, **2**, 1183.

anti-metabolites, is essentially based on careful studies of the target animal's biochemical make-up. It is hoped that firstly, an essential metabolic pathway could be discovered not present in related species, and secondly, that a chemical compound could be designed selectively to block this route. The compound so synthesized, even if it could reach the active site and in the form required, must possess the correct stability, palatability, and onset of action necessary for an efficient rodenticide. The anti-metabolite 6-amino-nicotinamide is currently being studied[28] as a candidate rodenticide. The biological evaluation of rodenticides is similarly a difficult task, and a clear account of the problems has been given by Bentley.[18]

The rodenticides used in baits may conveniently be divided into organic and inorganic compounds; the latter are usually considered as acute poisons while the former require subdivision into both acute and chronic poisons.

A. Bait Poisons.—(i) *Organic Compounds.* (*a*) *Acute rodenticides.* The acute rodenticides are those in which a lethal quantity of poison is ingested in a single dose in the food or drink of the rodent. Unfortunately, animals often consume a sub-lethal dose which, although insufficient to kill, still produces disturbing side effects. The animals associate these unpleasant symptoms with the poisoned bait and 'bait-shy' animals result which are unlikely to be killed with the same poison and bait combination. However, in some circumstances, *e.g.* where outbreaks of disease necessitate immediate control, acute poisons are preferred to the second type of rodenticide, the chronic kind. Most of the acute rodenticides require prebaiting techniques, for rodents need to be conditioned in order to overcome their shyness towards new objects. The unpoisoned bait is first presented to the rodent until the animal feeds regularly and then it is replaced by bait containing the poison.

Red squill is probably the oldest known rodenticide.[29] A detailed account of its historical and botanical origin and its toxicological properties has been presented.[5] Red squill may be extracted from the bulb of the lily-like plant *Urginea maritima*, common to the Mediterranean coastal area. A toxic principle, named scilliroside[8] (LD_{50} = 0.70 mg/kg, male white rats) has been isolated from the plant extract and assigned the structure (1).



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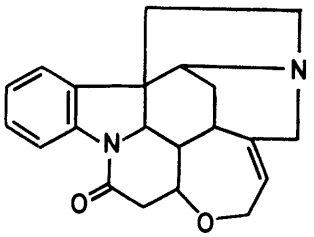
[28] Personal communication, Ministry of Agriculture, Fisheries, and Food.
[29] A critical review of the currently used acute rodenticides is given by N. G. Gratz. 'Seminar on Rodents and Rodent Ectoparasites', Geneva, 1966. (W.H.O. Vector Control, 66.217.)

The main disadvantage[30] of red squill as a rodenticide is the variation in potency of the extracted materials, which has necessitated the setting up of biological standardization tests based on rodenticidal activity.[29] Good control of *R. norvegicus* but only moderate control of *M. musculus* and *R. rattus* has been claimed,[31] using 0.5% stabilized scilliroside in baits.

The violent nature of rodent deaths caused by red squill poisoning has brought about the banning of this poison in the U.K. on humanitarian grounds.[32]

Strychnine (2) (LD_{50} = 50 mg/kg, *R. norvegicus*)[5] has been used as a



(2)

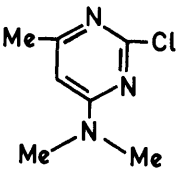
vertebrate pesticide since the seventeenth century. The bitter taste of the alkaloid seems to interfere with the success of rodent campaigns.[33] No advantages have been evident in employing strychnine salts.[33] The use of this compound in rodent control was banned[32] in 1935 in the U.K. although it is still employed for mole extermination.[34]

(3)

Antu, α-naphthylthiourea (3), which was the first synthetic organic rat poison,[35] may be prepared[36] by treating α-naphthylamine with ammonium thiocyanate. Particle size has an interesting effect on toxicity;[37] for an unknown reason, larger particles (50—55μ) are more toxic than smaller particles (5μ). Antu is primarily

[30] A. Mallis, 'Handbook of Pest Control, Rats and Mice', MacNair-Dorland Co., U.S.A., 1945, p. 13.
[31] D. R. Maddock and H. F. Schoof, *Pest Control*, 1970, **38**, 32.
[32] D. C. Drummond, *Chem. and Ind.*, 1966, 1371.
[33] W. A. McDougall, *Queensland J. Agric. Sci.*, 1944, **1**, 1.
[34] G. S. Hartley and T. F. West, 'Chemicals for Pest Control', Pergamon Press, Oxford and London, 1969, p. 139.
[35] C. P. Richter, *J. Amer. Med. Assoc.*, 1945, **129**, 927.
[36] S. B. Alvarez, *Rev. quim. farm.* (*Santiago, Chile*), 1947, **4**, 2.
[37] E. W. Bentley, Y. Larthe, and A. Taylor, *J. Hyg.* (*Cambridge*), 1955, **53**, 328.

effective against *R. norvegicus* (LD_{50} = 7 mg/kg) and considerably less lethal[38] to *R. rattus* and *M. musculus*. Sub-lethal doses cause a definite tolerance which is even evident a few hours after ingestion of the poison. Antu has now lost favour[27] as a rodenticide in the U.K.



(4)

Castrix, 2-chloro-4-dimethylamino-6-methylpyrimidine (4),[39] developed in Germany during the Second World War, is a powerful convulsive agent (LD_{50} = 1 mg/kg, albino rats), for which fortunately, there is an effective antidote, sodium pentobarbital. The poison is well accepted by rats[39] in baits at a concentration of 0.25—1.0% and against mice in grain baits it has proved most effective.[29] Preliminary trials against *Holochilus sciureus* have given promising results,[26] but field use against *R. norvegicus* was not satisfactory.[29]

Monofluoroacetic acid derivatives[40] have been screened by research workers of the United States Fish and Wildlife Service, following a lead from Polish chemists.[40,41] Number 1080 in their series was sodium fluoroacetate and 1081 fluoroacetamide. Independent work[42] led to the discovery of the potassium salt of monofluoroacetic acid as a component of the South African plant *Dichapetalum cymosum*, well known to be poisonous to livestock.

Sodium fluoroacetate is exceedingly toxic to man and all animals, especially dogs,[34] as well as to rodent pests (LD_{50} = 3—5 mg/kg, *R. norvegicus*).[29] Its lethality is due to the blocking[43] of the vital mammalian energy-releasing citric-acid cycle, and there is no specific antidote although glycerol monoacetate and other suggestions have been put forward.[40] Sub-lethal doses do not generally appear to lead to tolerance although cases of acquired resistance are reported.[40,41] Sodium fluoroacetate has found use in the control of rats in sewers[44] and ships.[45] In Australia,[46] sodium fluoroacetate has been used to control rabbits and in the United States,[47] to control ground squirrels. In the interests of safety[32] to man

[38] M. Lund, *World Rev. Pest Control*, 1967, **6**, 131.
[39] K. P. Dubois, K. W. Cochran, and J. F. Thomson, *Proc. Soc. Exp. Biol. Med.*, 1948, **67**, 169.
[40] M. B. Chenoweth, *J. Pharmacol.*, 1949, **97**, 383.
[41] E. R. Kalmbach, *Science*, 1945, **102**, 232.
[42] J. S. C. Marais, *Onderstepoort J. Vet. Research*, 1944, **20**, 67.
[43] R. Peters, R. W. Wakelin, and P. Buffa, *Proc. Roy. Soc.*, 1953, **B140**, 497.
[44] E. W. Bentley, 'Control of Rats in Sewers', Ministry of Agriculture, Fisheries, and Food, Tech. Bull., No. 10, 1960.
[45] J. H. Hughes, *U.S. Public Health Service Rep.*, 1950, **65**, 1021.
[46] C. S. Hale and K. Myers, *Int. Pest Control.*, 1970, **12**, 12.
[47] R. E. Marsh, Proceedings of the Third Vertebrate Pest Conference. California. ed. M. Cummings, 1967, p. 2.

and non-pest species, the sale and distribution of this otherwise effective rodenticide and its related compounds are now restricted[48] in the U.K.

The first suggestion for the use of fluoroacetamide as a rodenticide is attributed to Chapman and Phillips.[49] It is less toxic (LD_{50} = 13 mg/kg, *R. norvegicus*)[50] than fluoroacetate but proved more successful in field trials in sewers[51] at 2% bait concentration than sodium fluoroacetate at 0.25% or zinc phosphide at 2.5%. Similar restrictions apply to the use of this rodenticide.

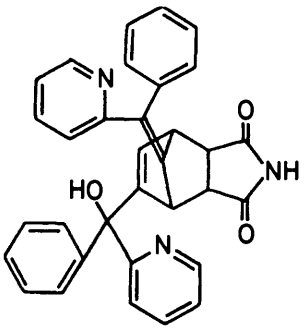
Many examples of monofluoroacetic acid (5), and monofluoroethanol derivatives (6), which possess similar toxicity, appear in the literature.[7,40,52–54]

FCH_2COR (5) R = NHNHPh, NHCH(CCl$_3$)·OCONHPh, NHCH(CCl$_3$)·NHPh, NHCH(CCl$_3$)·SR^1, or NHCH(CCl$_3$)·NHCONHR^1

R^1 = alkyl, aryl, *etc.*

$FCH_2CH(OH)R$ (6) R = H, CH_2F, or CH_2Cl

Norbormide, 5-(α-hydroxy-α-2-pyridylbenzyl)-7-(α-2-pyridylbenzylidene)norborn-5-ene-2,3-dicarboximide (7), as prepared commercially, exists as a mixture



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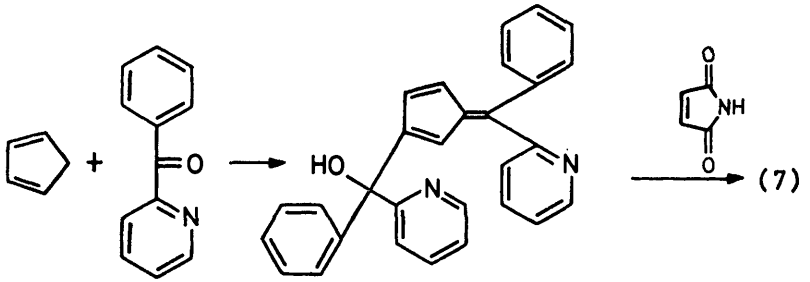
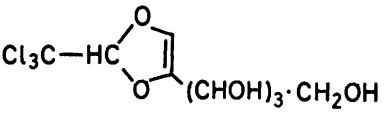
[48] 'Use of Fluoroacetamide and Sodium Fluoroacetate as Rodenticides; Precautionary Measures'. Ministry of Agriculture, Fisheries, and Food Leaflet, 1965.
[49] C. Chapman and M. A. Phillips, *J. Sci. Food Agric.*, 1955, **6**, 231.
[50] E. W. Bentley and J. H. Greaves, *J. Hyg. (London)*, 1960, **58**, 125.
[51] E. W. Bentley, *J. Hyg. (London)*, 1961, **59**, 413.
[52] L. Karel, *J. Pharmacol. Exp. Therap.*, 1948, **93**, 287.
[53] B. Y. Falkenshtein and I. P. Ershova, *Gigiena i Sanitariya*, 1957, **22**, 96.
[54] C. Fest and G. Hermann, *Pflanzenschutz Ber.*, 1969, **39**, 241.

of geometric and optical isomers[55] which collectively possess a highly specific toxicity to rats (LD_{50} = 9—12 mg/kg, *R. norvegicus*).[38] This material was the first known *Rattus*-specific toxic agent, for related genera such as *Mus*[38] and *Bandicota*[56] are to all intents and purposes immune. Norbormide was first synthesized[57] during a study of potential anti-rheumatic agents:



The stereoisomers were separated[58] by fractionation and chromatographic procedures and shown to vary widely in potency. Norbormide analogues have also been synthesized[58] for structure–activity studies. Substitution at any but the dicarboximide ring positions led to compounds less than one-twentieth as active as norbormide while compounds possessing substituents on the imide nitrogen atom displayed potencies ranging from about equivalent to that of norbormide to less than one-twentieth of this activity.

Only mediocre results have been obtained in rodenticide field trials, *e.g.* in New Zealand,[59] Wales,[60] and elsewhere.[29,61] This has been attributed to the rodent's ability to detect the presence of norbormide in the bait and to develop bait-shyness. In a comparative trial[60] *versus* zinc phosphide, norbormide was proven somewhat inferior, even when various concentrations, various cereal baits, and direct-baiting and pre-baiting techniques were used. In spite of these disappointing results, norbormide is an interesting development in rodent control and has been recommended[60] for use where risks to livestock are high.



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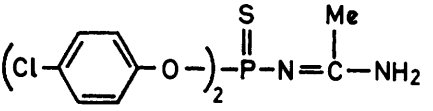
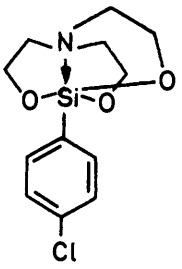
[55] A. H. Netherwood, *Agri. Vet. Chem.*, 1965, **6**, 115.
[56] P. J. Deoras, *Current Sci.*, 1965, **34**, 348.
[57] R. U. Russell, *J. Forensic Sci. Soc.*, 1965, **5**, 80.
[58] G. I. Poos, R. J. Mohrbacher, E. L. Carson, V. Paragamian, B. M. Puma, C. R. Rasmussen, and A. P. Roszkowski, *J. Med. Chem.*, 1966, **9**, 537.
[59] A. E. Beveridge and M. J. Daniel, *Proc. N.Z. Ecolog. Soc.*, 1966, **13**, 40.
[60] B. D. Rennison, L. E. Hammond, and G. L. Jones, *J. Hyg. (Cambridge)*, 1968, **66**, 147.
[61] D. R. Maddock and H. F. Schoof, *Pest Control*, 1967, **35**, 22.

α-Chloralose (8) is a recently introduced acute poison.[62] It acts by retarding the animal's metabolic processes, so that the animal dies from hypothermia. This substance is thus more effective at temperatures below 15 °C and is more specific to small animals such as mice (LD_{50} = 300 mg/kg at 10—18 °C)[62] because of their larger surface-area to volume ratio. Restrictions on the placement of poisoned baits exist[63] since this poison is hazardous to birds. The effects of microencapsulation have been examined[64] and work concerned with devising improved formulations is under way.



(9)

Gophacide, *OO*-bis-(*p*-chlorophenyl)acetimidoylphosphoramidothioate (9), a new cholinergic rodenticide, has been found to be of value in the control of deermice (*Peromyscus maniculatus*)[65] and pocket gophers[66] (*Thomomys talpoides*, *Geomys bursarius*, and related species). Field trials *versus R. norvegicus*, *R. rattus*, and *M. musculus* with baits containing the poison at 0.2—0.5% concentration have generally given favourable results.[67] The acute toxicity and mechanism of action have been described,[68] and atropine and pralidoxine have been suggested as antidotes.[66]



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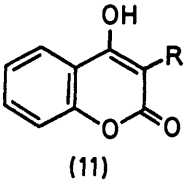
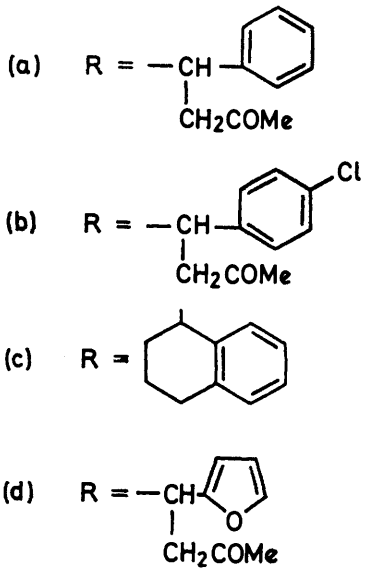
[62] P. B. Cornwell, *Pharm. J.*, 1969, **202**, 74.
[63] 'Alphakil—A New Rodenticide for Mouse Control', Rentokil Laboratories Ltd., Tech. Release, 1966, 66/2.
[64] P. B. Cornwell, *Int. Pest Control*, 1970, **12**, 35.
[65] M. C. Hoffer, P. C. Passof, and R. Krohn, *J. Forestry*, 1969, **67**, 158.
[66] V. B. Richens, Proceedings of the Third Vertebrate Pest Conference, California, ed. M. Cummings, 1967, p. 118.
[67] Anon. *Pest Control*, 1969, **37**, 15.
[68] K. P. Dubois, F. Kinoshita, and P. Jackson, *Arch. Internat. Pharmacodyn.*, 1967, **169**, 108.

Silatrane, 1-(*p*-chlorophenyl)-2,8,9-trioxa-5-aza-1-silabicyclo[3,3,3]undecane (10), is another recently reported[69] acute poison (LD_{50} = 1—4 mg/kg, lab. rats). It is claimed to be an effective fast-acting control agent exhibiting no secondary hazards, since rapid detoxification occurs after ingestion. Field studies[69] are in progress to assess its usefulness for control of rats, ground squirrels, and mice.

(*b*) *Chronic rodenticides.* Chronic rodenticides bring about the death of the rodent only after the poisoned bait has been consumed on a number of occasions. The symptoms of poisoning are so delayed that the animal never learns to associate discomfort with bait consumption and continues to feed until a lethal dose has been ingested. The cumulative, slow-acting nature of these materials is characteristic of this type of poison, hence their respective LD_{50} values do not reflect a chronic poison's potential killing power. For example,[70] *R. norvegicus* survived single 50 mg/kg doses of the anticoagulant warfarin, but succumbed to 5 consecutive doses of 1 mg/kg taken on successive days. The main compounds possessing a chronic poisoning action are the anticoagulants, which interrupt the synthesis of blood-clotting factors so that poisoned animals die from internal bleeding. Other substances with chronic poisoning properties but with different modes of action are also known, *e.g.* trifluorobenzimidazoles[71] and quinoline disulphides.[72] The evaluation of chronic rodenticides has been discussed by Bentley.[18]

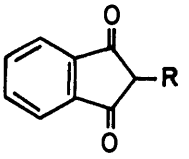


(11)



[69] C. B. Beiter, M. Schwarcz, and G. Crabtree, *Soap*, 1970, **46**, 38.
[70] W. J. Hayes and T. B. Gaines, *Publ. Health Rep., Wash.*, 1950, **65**, 1537.
[71] South African P. 8004/1969.
[72] Unpublished researches. Lilly Research Centre Ltd., Ministry of Agriculture, Fisheries, and Food.

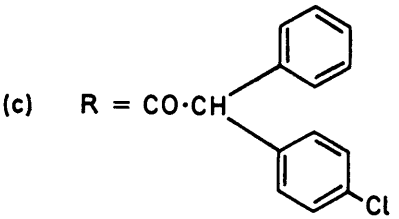
Anticoagulant rodenticides are either coumarin (11) or indanedione (12) derivatives.



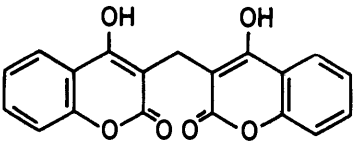
(12)

(a) R = CO·CMe$_3$

(b) R = CO·CH(Ph)$_2$



Some early studies in the United States to discover the cause of sweet-clover disease in cattle led to the isolation of 3,3′-methylene-bis-4-hydroxycoumarin [dicoumarin, (13)].[73] This compound was found to make the blood clot more



(13)

slowly than normal and was immediately recognized to be of value in human medicine for alleviating conditions such as coronary thrombosis. The synthesis of other, related compounds followed and the 42nd substance described in the report[74] by Links' group was more effective than dicoumarin. This compound later became known by its generic name, warfarin; the first four letters being derived from Wisconsin Alumni Research Foundation, to whom the patent rights were assigned.

In 1948, a report by O'Connor[75] appeared on the merits of the multiple-dose technique that had proven successful with dicoumarin. This discovery added fresh impetus to research efforts in the anticoagulant field. A number of other haemorrhagic agents were tested subsequently and the rodenticidal action of 1,3-indanediones was discovered.[76] The near ideal situation in rodent

[73] M. A. Stahmann, C. F. Huebner, and K. P. Link., *J. Biol. Chem.*, 1941, **138**, 513.
[74] R. S. Overman, M. A. Stahmann, C. F. Huebner, W. R. Sullivan, L. Spero, D. G. Doherty, M. Ikawa, L. Graf, S. Roseman, and K. P. Link. *J. Biol. Chem.*, 1944, **153**, 5.
[75] J. A. O'Connor, *Research. London*, 1948, **1**, 334.
[76] H. Kabat, E. F. Stohlman, and M. I. Smith, *J. Pharmacol.*, 1944, **80**, 160.

control brought about by the introduction of anticoagulants has now changed, however, with the appearance of genetically based resistance.[38]

The anticoagulants possess certain general properties,[6] *e.g.*:

(*a*) No bait shyness; animals ingest bait until death.

(*b*) No prebaiting is necessary as acceptance of poisons is good at lethal concentrations.

(*c*) Low dosages are effective, *e.g.* warfarin used at 0.005—0.25% in prepared baits.

(*d*) They are relatively non-toxic to domestic animals and man, although the view that they are without risks of any kind is erroneous.

(*e*) Accidental poisoning can be controlled by the prompt use of Vitamin K.

A number of accounts of the relative merits and demerits of individual anticoagulants have appeared[77–84] but only a few specific properties of individual rodenticides will be discussed here.

Warfarin, 3-(1-phenyl-2-acetylethyl)-4-hydroxycoumarin (11a), may be synthesized[85] by a Michael condensation between benzalacetone and 4-hydroxycoumarin in the presence of a base such as piperidine. The product is a racemic mixture which exhibits reactions typical of its functional groups. Warfarin is the most widely used anticoagulant[77] for the control of *R. norvegicus* and *M. musculus*, and satisfactory results have been reported with *R. rattus* and in trials against other rodent pests.[77,86] Dangers to non-pest species, although minimal, are, however, not entirely absent.[87]

Poisoning techniques involving warfarin have been extensively studied. In locations deficient in water supplies the sodium salt can be effective when presented to rodents in their drinking water.[8] In solid baits it has been found[18] that smaller particles lower the acceptance. Protection and preservation of baits in wax formulations and paper-wrapped baits is common practice under some adverse conditions.[88] Other poisoning techniques have been described, for example the use of warfarin in contact dusts,[89] foams,[90] and aerosols.[91]

Other important coumarins are coumachlor (11b), coumatetralyl (11c), and fumarin (11d).

[77] E. W. Bentley, 'Review of Currently Used Anticoagulants', Seminar on Rodents and Rodent Ectoparasites, Geneva 1966 (W.H.O. Vector Control, 66.217), p. 89.
[78] J. H. Greaves and P. Ayres, *J. Hyg. (Cambridge)*, 1969, **67**, 311.
[79] E. W. Bentley and T. Larthe, *J. Hyg. (Cambridge)*, 1959, **57**, 135.
[80] F. P. Rowe and R. Redfern, *Ann. Appl. Biol.*, 1968, **62**, 355.
[81] J. P. Saunders, S. R. Heisley, A. D. Goldstone, and E. C. Bay, *J. Agric. Food Chem.*, 1955, **3**, 762.
[82] F. P. Rowe and R. Redfern, *Ann. Appl. Biol.*, 1968, **61**, 322.
[83] E. W. Bentley and M. Rowe, *J. Hyg. (Cambridge)*, 1956, **54**, 20.
[84] W. J. Hayes and T. B. Gaines, *Publ. Health Rep., Wash.*, 1959, **74**, 105.
[85] M. Seidman, D. N. Robertson, and K. P. Link, *J. Amer. Chem. Soc.* 1950, **72**, 5193.
[86] J. C. Taylor, H. G. Lloyd, and J. F. Shillito, *Ann. Appl. Biol.* 1968, **61**, 312.
[87] D. S. Papworth, *Roy. Soc. Health J.*, 1958, **78**, 52.
[88] R. A. Gillbanks, P. D. Turner, and B. J. Wood, *The Planter*, 1967, **43**, 297.
[89] F. P. Rowe and A. H. J. Chudley, *J. Hyg. (Cambridge)*, 1963, **61**, 169.
[90] V. G. Zatsepin, *Trudy Vses. Nauchn.-Issled. Inst. Vet. Sanit.*, 1966, **25**, 357.
[91] Fr.P. 1 489 813 (*Chem. Abs.*, 1968, **68**, 104 137v.).

Coumachlor, 3-(1-*p*-chlorophenyl-2-acetylethyl)-4-hydroxycoumarin (11b), is similar to warfarin but somewhat less useful against *R. norvegicus*.[79] It has been used effectively as a contact dust.[8] Coumatetralyl,[92] 4-hydroxy-3-α-tetralylcoumarin (11c), and fumarin[79], 3-(2-acetyl-1-furylethyl)-4-hydroxycoumarin (11d), have proved good alternatives to warfarin for the control of rats and mice.

Pival, 2-pivalyl-1,3-indanedione (12a), may be prepared[93] by means of a Claisen condensation between diethyl phthalate and pinacolone. It was synthesized as part of a study aimed at comparing insecticidal activity with variations in 1,3-indanedione structure. An account of the early development of this compound as a rodenticide has been given by Mills.[9] Studies[83] have indicated that pival is a useful alternative to warfarin against *R. rattus*. An advantage over warfarin is the insecticidal[93] and fungistatic action of pival that retards the deterioration of prepared baits. Other indanedione derivatives, diphacinone (2-diphenylacetyl-1,3-indanedione) (12b),[94] chlorophacinone {2-[1-(*p*-chlorophenyl)-1-phenyl]acetyl-1,3-indanedione} (12c),[95,96] *etc.*, have found use as rodenticides.

(ii) *Inorganic Compounds.* In general these compounds are non-selective in action and for this and other reasons are not frequently used. One poison, however, zinc phosphide, has held its place and proved valuable for the extermination of rats resistant to warfarin.

Zinc phosphide (Zn_3P_2) is a greyish-black powder (LD_{50} = 40 mg/kg, *R. norvegicus*)[18] possessing a strong disagreeable odour which, surprisingly, does not deter rats and is sometimes said to possess certain attractive properties. Nevertheless, the prebaiting technique is still required. The instability of zinc phosphide in the presence of moisture can cause deterioration of poisoned baits.[97] For longer-lasting effects, baits are sometimes wrapped in waxed[2] or waterproof paper, or mixed with mineral oil[29,97] rather than water. In the U.K., cereal baits such as soaked wheat or medium oatmeal containing zinc phosphide (2.5%) have been used successfully.[1] The advantages of low secondary toxicity and low cost together with its fairly good safety record have contributed to the widespread use of this poison.[29] Cases of acquired resistance have been found with the species *R. rattus*[38] and *B. bengalensis*.[98]

Arsenious oxide (arsenic trioxide, As_2O_3), also known as 'white arsenic', has a toxicity that is dependent upon the particle size, *e.g.* for white rats LD_{50} = 60 mg/kg at $<5\mu$ diameter but 148 mg/kg at $>100\mu$.[18] Arsenious oxide was one of the earliest rodenticides, but its use has decreased rapidly of late due to general restrictions on the sale of arsenic-containing compounds[29] and to poor

[92] I. F. Thompson, *Baywood Courier*, 1969, **3**, 10.
[93] L. B. Kilgore, J. H. Ford, and W. C. Wolfe. *Ind. and Eng. Chem.*, 1942, **34**, 494.
[94] R. L. Gates, *Pest Control*, 1957, **25**, 14.
[95] J. Tahon, *Parasitica*, 1969, **25**, 167 (*Chem. Abs.*, 1970, **73**, 55 009x).
[96] R. Moens and A. Ghesquiere, *Rev. Agr.* (*Brussels*), 1969, **22**, 1089 (*Chem. Abs.*, 1970, **72**, 89 249v).
[97] H. F. Schoof, *Pest Control*, 1970, **38**, 38.
[98] A. S. Srivastava, *Labdev. J. Sci. Tech.*, 1967, **5**, 168.

and erratic levels of acceptance by rodents. Acquired tolerance to this rodenticide has been reported.[38]

Thallous sulphate (Tl_2SO_4), a cumulative poison which exhibits no warning properties,[30] is in some ways a most effective rodenticide (LD_{50} = 16 mg/kg, *R. norvegicus*)[18] but its use is limited by serious human health hazards. It is dangerous not only as a direct poison, but also because it is absorbed through the skin.[8] Secondary poisoning is also possible, and sub-lethal doses induce sterility[88] and other effects.[33] An antidote employing dimercaprol and methionine has been described,[99] but cases of thallium poisoning have been so widespread that, although excellent results can be achieved in controlling rodents, it is now banned in many countries for general use.[6,88]

B. Poison Dusts.—Dust formulations of lethal substances possess properties useful in rodent-control programmes, *e.g.* the placing of calcium cyanide dust in the holes and burrows of rodents is a useful procedure in fumigation work.[34] Another technique involves the use of contact dusts,[8] a method [100] which appears to have arisen accidentally from studies with the insecticides D.D.T. and B.H.C. This method overcomes possible idiosyncrasies in feeding behaviour for it depends upon the rodent inadvertently coming into contact with the dust laid in rodent-frequented areas. It is possible for a lethal dose of a poisonous dust to be eventually ingested by a rodent, for any material that has adhered to its feet and fur is transferred to its mouth during normal cleaning and grooming activity. This method therefore requires concentrations of poisons far higher than that used in baits, for the animal can only be expected to consume small amounts during grooming. A typical poison dust[8] consists of an inert, finely divided material, a suitable poison with sometimes an adhesive, a water-repellant, and a warning dye.

The advantages of contact dusts are that rodents do not suspect the source of illness resulting from ingestion and so do not avoid normal travel routes. Further, it is not necessary to persuade animals to change their feeding habits as with poison baiting. There are several disadvantages, which explain why this technique is not in frequent use. Firstly, there is the danger aspect that prevents use near human or animal foodstuffs because of the risk of contamination. Their correct placement is also necessary so as to be away from areas traversed by other animals, *e.g.* cats and dogs. All the routes which rodents frequent need to be located. The use of poison dusts is also uneconomic, for much material must be laid even though only a small amount will be removed and consumed by the rodent. The dust should also be fine enough to stick to feet and fur, yet not to be so light as to be moved by air currents.

Warfarin[89] and other anticoagulants, coumachlor,[8] coumatetralyl,[92,101] *etc.*

[99] W. Schild and A. Schrader. *Nervenarzt, Heidelberg*, 1952, **23**, 288; *J. Amer. Med. Assoc.* 1952, **150**, 1730.
[100] E. E. Turtle and A. Taylor, *Reports Progr. Appl. Chem.*, 1955, **40**, 680.
[101] N. Dudley, *Bayer Agro Chem. Courier*, 1970, **3**, 11.

are normally used at *ca.* 1% concentration for the purposes of rat and mouse control.

D.D.T. in micronized form in concentrations ranging from 20 to 50% has been used against *M. musculus*.[102] Lindane at a similar concentration has been claimed more effective than either warfarin or D.D.T.[103] Chemosterilants may also be presented to rodents in contact dust formulations.[15]

C. Fumigants.—Infestations in warehouses, foodstores, and granaries do not always respond satisfactorily to poison baiting, trapping, and other direct control methods. The main problem is the difficulty of getting the rodent to break cover, for sometimes an apparently attractive bait is not a sufficient lure. Situations like these and others, where direct control is impracticable or unsuccessful, may often benefit by the application of fumigation techniques. The penetrating properties of fumigants allows rodent extermination to proceed even in inaccessible areas.

There are a number of volatile substances and gases that could be suggested as fumigants but the choice is narrowed when toxicity, diffusion, adsorptive characteristics, and possible side effects are considered. For instance, in buildings containing foodstuffs and other stored commodities, fumigation treatment must not produce any permanent deleterious side-effects through absorption of the fumigant.

In the U.K.,[1] the most frequently encountered fumigants are hydrogen cyanide and methyl bromide, to which chloropicrin,[104] a powerful lachrymator, is sometimes added as a warning agent. Sulphur dioxide,[104] although cheaper than some other fumigants, has proved inferior because of poor penetrating properties and corrosive effects. Carbon dioxide[5,105] in the form of 'dry-ice' is a convenient and safe method but suffers from being more expensive and difficult to apply than alternative fumigants. A number of other gases and volatile liquids have been investigated, *e.g.*, carbon disulphide,[106] ethylene oxide,[107] carbon monoxide,[108] and others.[1,104,109]

The extermination of outdoor colonies of rodents is normally carried out with hydrogen cyanide gas.[1,30,34] It is customary to blow or inject calcium cyanide in granular or dust form into a burrow so that when it comes into contact with moist air or soil the gas is liberated. Since hydrogen cyanide is lighter than air, greater concentrations of gas collect in higher areas of the burrow network, so for this and other more obvious reasons, all holes need to be rapidly sealed up.

[102] 'Insecticide Resistance and Vector Control', W.H.O. Tech. Report Series No. 443, 1970, p. 241.
[103] Rentokil Laboratories Ltd., Tech. Release, 1969, 69/1.
[104] Ref. 34, p. 274.
[105] R. H. Thompson, *Pest Technology*, 1959, **2**, 7.
[106] E. R. Kalmbach, F.A.O. Agric. Studies No. 2, Rome, 1962, 149.
[107] R. H. Thompson and E. E. Turtle, *Chem. and Ind.*, 1953, 365.
[108] S. W. Porritt, D. V. Fisher, and E. D. Edge, *Proc. Amer. Soc. Hort. Sci.*, 1952, **60**, 265.
[109] 'A Critical Appraisal of Rodenticides', S. K. Majumder, M. K. Krishnakumari, and K. Muktabai, Indian Rodent Symposium, Calcutta, 1966.

Methyl bromide has also been widely used in burrow fumigation[110] and one technique employs ampoules containing the volatile liquid which are carefully broken deep in the burrow system. A more recent approach has been the use of fumigant emulsions.[109] Injection into the burrow system of emulsions based on ethylene dibromide or chloropicrin, with water acting as the vehicle, has given good results.

6 Baits and Additives

However toxic a chemical poison might be, it will not be lethal unless a rodent of its own volition consumes a lethal dose, which can only occur if the animal visits the spot where the poisoned bait is placed. This demands a high 'rodent appeal' from a particular bait, great enough to compete successfully with any other attractive food available to the animal.

The bait chosen depends upon a number of factors, *e.g.* the pest species, the environment in which baiting is to be attempted, the bait's keeping qualities, and convenience in handling. Baits that have been employed[111] cover the complete range of foodstuffs available but in the U.K. cereal baits have found the greatest use, particularly baits based on oatmeal.[112] Unfortunately, although the testing of unpoisoned baits on wild rodents can indicate a preferred bait, it is often not the bait of choice when the poison is added.[113]

In a poisoned bait, apart from the toxic ingredient and the bait itself, other additives are sometimes included in the formulation to improve performance. The changes in palatability resulting from the inclusion of certain additives may result in their eventual exclusion even though other beneficial properties might otherwise have been imparted.

A. Attractants.—Attractants are substances which lure the animal to the poisoned bait. Strictly, attractants have only this property of enticement and do not necessarily increase the uptake of the bait by the animal. Many of these materials, however, have other properties, such as taste enhancement or masking actions and so a certain degree of ambiguity in terminology has arisen. Fresh raw linseed oil[33] is an example of a simple attractant which attracts a rat but does not result in an increase in bait consumption. Various flavourings, essences, and oils are claimed to have attractant properties, *e.g.* arachis oil,[114] although some may actually act as repellants,[115] *e.g.* aniseed oil.[116] Certain odourless oils are taste accentuators; for instance it is claimed[117] that the scent of a wheat bait containing an anticoagulant poison may be improved with mineral oils.

[110] P. J. Deoras, *Current Sci.*, 1960, **29**, 475; *ibid.* 1962, **32**, 163.
[111] E. M. Mills. *Pests* 1942, **10**, 6.
[112] P. B. Cornwell and J. O. Bull, *Pest Control*, 1967, **35**, 15.
[113] H. R. Shuyler, 'The Development of Baits for *Rattus norvegicus*', Ph.D. Thesis, Purdue University, 1954.
[114] S. A. Barnett and M. M. Spencer, *J. Hyg. (Cambridge)*, 1953, **51**, 16.
[115] D. C. Drummond, 'Repellants and Attractants and their role in the control of Rodents', International Symposium on Bionomics and Control of Rodents, Kanpur, 1968.
[116] S. A. Barnett and M. M. Spencer, *Brit. J. Anim. Behav.*, 1953, **1**, 32.
[117] J. Sims, *Pest Control*, 1964, **32**, 90.

Additives that confer their own flavour to a bait may be 'attractants' or secondary foods[111] such as sugar, *etc.* Maltose at a 2—30% concentration is considered[118] to improve palatability of various bait compositions. Dexide, a carbohydrate with flavour material, has been reported[119] to increase consumption of warfarin-containing baits.

B. Potentiating Agents.—To enable anticoagulants to be toxic to warfarin-resistant rodents, various potentiating agents have been sought. Since Vitamin K competes with warfarin for the same enzyme site, introduction of a Vitamin K antagonist should permit warfarin to be more lethal. Various compounds have been incorporated in baits to fulfil this role; salicylic acid, 2-methoxy-1,4-naphthoquinone, *etc.*[120] Antibiotics, *e.g.* 5-hydroxytetracycline, that destroy Vitamin-K-producing bacteria, have also been included[120] as well as various sulphonamides, *e.g.* sulphaquinoxaline.[119] Anti-Vitamin C compounds, *e.g.* D-gluco-ascorbic acid, that increase the permeability of the capillaries have been utilized[121] to accentuate the action of the anticoagulants. Synergistic effects have been claimed following the addition of hydrofurfuramide to anticoagulant baits[122] and the combination of thallium salts with various coumarins or indanediones.[123] In spite of these researches no breakthrough in the treatment of resistant rats has been made.

C. Formulation Additives.—(i) *Preservatives.* Studies have shown that *p*-nitrophenol[124] is a satisfactory mould-inhibitor in oat baits. This chemical, like dehydroacetic acid and its sodium salt, has been recommended[44,125] as a bait additives in poison baiting of rats in sewers. Sodium sulphate was the best of a number of compounds examined by the U.S. Fish and Wildlife Service for bait-preservative action.[111] A bait containing an insecticide could confer distinct advantages on a formulation to be used in tropical climates. D.D.T. and other insecticides have been examined in baits that tend to be infested by insect pests during storage.[126] Two rodenticides that have insecticidal properties are the anticoagulant pival[93] and sodium fluoroacetate.[127]

(ii) *Binders.* A poisoned bait should remain homogenous, and as an aid to maintaining uniform distribution it is the practice to add a 'binder' or 'sticker' to hold the components together, *e.g.* water, syrup, or mineral and vegetable oils.[111,128] To protect baits physically from deterioration, the preparation of baits set in wax has proved rewarding.[88] The high melting point of the wax

[118] B.P. 1 180 005/1970.
[119] R. M. Schisla, J. D. Hinchen, and W. C. Hammann, *Nature*, 1970, **228**, 1229.
[120] S. A. Span, 301 149/1964, (*Chem. Abs.*, 1965, **63**, 7606*a*).
[121] Belg. P. 642 725/1964 (*Chem. Abs.*, 1965, **63**, 6266*c*).
[122] Belg. P. 660 094/1965 (*Chem. Abs.*, 1965, **63**, P18 967*h*).
[123] T. Kusano, *J. Fac. Agri. Tottori Univ.* 1969, **5**, 15. (*Chem. Abs.*, 1971, **74**, 22 136*d*).
[124] R. E. Doty and C. A. Wismer, *The Hawaiian Planters Record*, 1949, **2**, 65.
[125] T. Larthe, *The Sanitarian*, 1957, **65**, 276.
[126] R. W. Smith, *Research Dept., Coconut Ind. Board (Jamaica)*, 1970, 68.
[127] W. A. L. David, *Nature*, 1950, **165**, 493.
[128] B. F. Bjornsen, H. D. Pratt, and K. S. Littig, 'Control of Domestic Rats and Mice', U.S.D.H.E.W. No. 563, 1969.

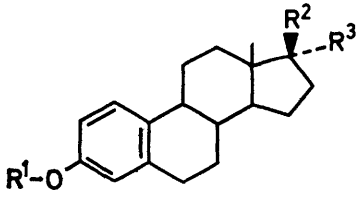
allows these baits to be used in tropical climates and their high resistance to sun and rain ensures a longer period of usefulness.

(iii) *Safety Additives.* To guard against accidental consumption of the poisoned bait by non-target species, it is often the practice to incorporate an emetic agent since rodents are unable to vomit. Tartar emetic[102] is generally used, but as responses of humans are variable and acceptability of these baits by rodents has been adversely affected in some cases, *e.g.* zinc phosphide,[67,97] these methods are not totally satisfactory. In many countries a colouring matter is required by law, to draw attention to a bait that contains a poison. Dyes such as prussian blue,[111] methylene blue,[33] and others[129] appear to exhibit no adverse effects on baits, although this is not invariably the case.[130]

7 Chemosterilants

An alternative approach to a solution of the rodent pest problem is through biogenetic control. The size of an infestation may be reduced to the point of virtual extinction when infertile animals are present in that community. This is possible since these animals are still able to assert their claim to territorial rights, food, and social order position, although they cannot contribute to the birth rate. Infertility may be introduced in a number of ways,[14] but the only practical way of implementing biogenetic control is through the use of chemosterilants.[15] To deploy chemosterilants effectively, information concerning the breeding cycle and reproductive behaviour of the pest species should be known, and, as in other control measures, ecological aspects must also be considered. Introduction of chemosterilants alone without any preliminary control measures, would probably be unsatisfactory on account of their slowness of action, so a combination of a chemosterilant with a selective rodenticide would appear to be a more satisfactory approach.

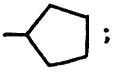
In the female of the species, a number of steroids have been examined. The oestrogen mestranol (14a), once considered to be of promise, was not satisfactory in trials[131] with *R. norvegicus* because of the attendant problems of bait shyness. Other derivatives (14b)[132a] and quinestrol (14c)[13,132b] have been claimed to be more effective.



(14)

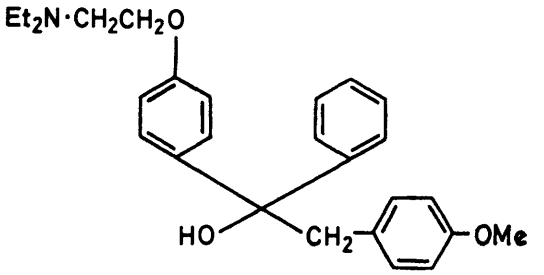
(a) $R^1 = Me$; $R^2 = OH$; $R^3 = C{\equiv}CH$;

(b) $R^1 = CH_2 \cdot C{\equiv}CH$; $R^2 = OCOCMe_3$; $R^3 = H$;

(c) R^1 =  ; $R^2 = OH$; $R^3 = C{\equiv}CH$;

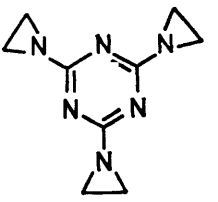
[129] W. W. Dykstra, *Pest Control*, 1950, **18**, 9.
[130] Y. Larthe, *J. Mammal.*, 1958, **39**, 450.
[131] R. E. Marsh and W. E. Howard, *J. Wildlife Management*, 1969, **33**, 133.
[132] (*a*) U.S.P. 3 496 272/1970; (*b*) U.S.P. 3 655 889/1972.

Some non-steroidal compounds able to terminate pregnancy are derivatives of clomiphene, *e.g.* MER-25 (15)[133] and diphenylindene.[134a]

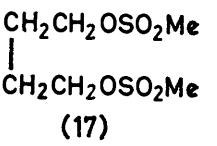


(15)

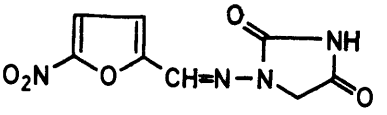
In practice it is more convenient to deal with the male animal, where the main work has been directed towards anti-spermatogenic agents. Alkylating agents[135] that only exert specific reproductive effects include compounds containing the ethyleneimine and methanesulphonate functional groups, for which compounds (16) and (17) serve as examples. Triethylenemelamine (16) has been examined in trials with rats,[136] but has recently lost favour[13] as a chemosterilant. Certain heterocyclic compounds[134b] exhibit anti-spermatogenic effects and a nitrofuran derivative, furadantin (18), when combined with colchicine, has been successfully used in field studies against *B. bengalensis*.[137]



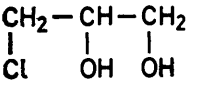
(16)



(17)



(18)



(19)

[133] S. J. Segal and W. O. Nelson, *Proc. Soc. Exp. Biol. Med.*, 1958, **98**, 431.
[134] (*a*) H. Jackson, 'Antifertility Compounds in the Male and Female', C. C. Thomas, Illinois, U.S.A., 1966, p. 176; (*b*) *ibid.*, p. 100.
[135] H. Jackson and A. W. Craig, *Ann. New York Acad. Sci.*, 1969, **160**, 215.
[136] D. E. Davis, *Trans. North Amer. Wildlife Conference*, **1961**, **26**, 160.
[137] A. S. Srivastava, *Labdev J. Sci. Tech.*, 1966, **4**, 178.

Another recent advance has been the discovery[138] that chlorohydrins, *e.g.* (19), induce sterility in the male rat. The advantages of relatively fast effects with non-toxicity to other forms of wildlife have been claimed although the precise mode of action has not yet been ascertained.

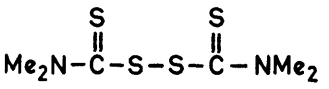
8 Repellants

An alternative form of rodent control is one based on repellency effects, which, although generally less satisfactory than other methods, is particularly useful where rodent damage is the central problem. The main draw-back in the use of repellants lies in the fact that rodents are not destroyed and at best are only diverted elsewhere.

Repellency effects created by physical stimuli have been described,[115] *e.g.* u.v. light[139] and high-intensity sounds,[140] but it is chemical stimuli that have received the most attention. It is well known that rodents are particularly sensitive to odours and tastes and it has been shown[10,141–143] that a number of substances found to possess repellent properties exhibit structure–activity relationships, *i.e.* repellency may be correlated with specified functional groups attached to certain cyclic and acyclic systems.

For the purposes of simplification, three main problem areas may be distinguished, *i.e.* (A) agriculture, forestry, and open areas, (B) packaged materials and stored products, and (C) wiring and cables. These sections are briefly described below, together with a few examples of repellants found useful in these situations.

A. Agriculture.—The destructive activities of rodents, namely gnawing, burrowing, and the search for food, cause much damage[12] to agricultural crops, seedlings, and trees. Taste repellants are particularly useful where a part of a plant or seedling is actually consumed. The properties that need to be associated with these repellants are: effectiveness throughout the whole season, no difficulties in application, no damage to plants or trees, and further, no toxicity to non-pest species.

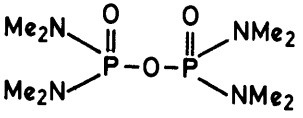


(20)

The historical development and usefulness of thiram, bis(dimethylthiocarbamyl) disulphide (20), as an animal repellant has been reviewed.[144] Experiments

[138] R. J. Ericsson and V. F. Baker, *J. Reprod. Fert.*, 1970, **21**, 267.
[139] E. J. Wilson, *Parasitica*, 1960, **16**, 119.
[140] C. M. Sprock, W. E. Howard, and F. C. Jacob, *J. Wildlife Management*, 1967, **31**, 738.
[141] E. Bellack and J. B. Dewitt, *J. Agric. Food Chem.*, 1954, **2**, 1176.
[142] J. E. Fearn and J. B. Dewitt, *J. Agric. Food Chem.*, 1965, **13**, 116.
[143] J. E. Fearn and J. B. Dewitt, *J. Pharm. Sci.*, 1964, **53**, 1269.
[144] M. A. Radwan, *Forest Sciences*, 1969, **15**, 439.

have shown that this repellant can confer protection from rodent attacks to seeds[145] and to trees *e.g.* Douglas Fir seedlings may be protected from rabbits,[146] hares, and mice.[147] The monosulphide derivative also shows repellent action to rodents.[144]



(21)

OMPA, octamethylpyrophosphoramide (21)[148], is a toxic systemic animal repellant which can be readily incorporated into plant tissue. The onset of phytotoxicity to Douglas Fir seedlings is well above the concentration required for repellency.[149]

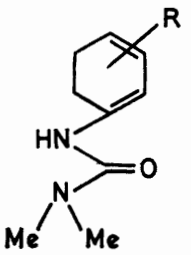
A large number of amine complexes with symmetrical trinitrobenzene exhibited high repellency indices in laboratory tests.[150] The aniline complex (TNB-A) was one of the most effective and has been used to protect seedlings and trees.[147]

The cyclohexylamine complex of zinc dimethyldithiocarbamate, $Zn(S_2CNMe_2)_2$, has been shown to reduce rodent damage to trees, seedlings, and plants.[10,147] An adhesive, polyethylene polysulphide, can be incorporated to prevent losses due to rain.[11]

Rodents that cause damage by burrowing, *e.g.* moles, mice, *etc.*, avoid soil contaminated with certain chemicals such as benzene hexachloride.[10] Introduction of suitable substances into the soil of ditch-banks as protection from pocket gophers has been found to have possibilities[10] whereas calcium carbide is recommended[151] for repelling muskrats from embankments. Herbicides can also influence certain rodent populations through the removal of rodent cover.[10] Field mice were found[152] to cease injuring apple trees after treatment of the adjacent plant growth with monuron (22a)[153] or diuron (22b).

B. Packaging.—Damage to packaging materials, boxes, sacks, and stored articles and products are frequently caused by rodents in their quest for cover and food. The established eradication and proofing techniques constitute the best approach, although alternative secondary measures, such as incorporation

[145] F. M. Johnson, J. Stubbs, and R. A. Klawitter, *J. Wildlife Management*, 1964, **28**, 15.
[146] A. C. Hildreth and G. B. Brown, U.S. Dept. of Agric., Tech. Bull. No. 1134, 1955.
[147] J. F. Besser and J. F. Welch, *Trans. North Amer. Wildlife Conference*, 1959, **24**, 166.
[148] A. D. F. Toy and E. N. Walsh, *Inorg. Synth.*, 1963, **7**, 73.
[149] J. H. Rediske and W. H. Lawrence, *Forest Science*, 1964, **10**, 93.
[150] J. B. Dewitt, E. Bellack, and J. F. Welch, *J. Amer. Pharm. Assoc.*, 1953, **42**, 695.
[151] 'Controlling Muskrats', United States Dept. of Interior, Fish and Wildlife Service, Leaflet No. 306, 1966.
[152] L. Holm, F. A. Gilbert, and E. Haltrick, *Weeds*, 1959, **7**, 405.
[153] G. L. McCall, *Agric. Chem.*, 1952, **7**, 40.

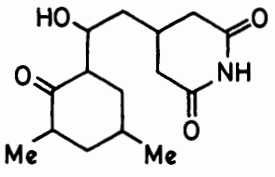


(a) R = 4-chloro

(b) R = 3,4-dichloro

(22)

of repellent substances into the packaging material, may deter or retard rodent attacks. A quantitative method has been devised[154] for evaluating chemicals as rodent repellants on packaging materials. Apart from repellency, there are rigorous requirements for potential repellent substances.[10] These include stability, no objectionable taste or odour, and the absence of toxic properties. The absence of any adverse effects on packaging materials or enclosed articles is especially critical. Some recent advances have been made in this area, particularly where repellant-treated fabrics enclosed between two layers of polyethylene protect both food and handler.[155]

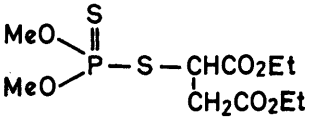


(23)

Actidione, (cycloheximide), 4-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]glutarimide (23), is a very effective rat-repellant.[10,156] Under simulated field conditions all rodent attacks upon treated paper board and cartons were repelled. Unfortunately, this repellant is too toxic to be permitted to come into contact with man's food or with his skin through package handling, which together with its high cost, probably accounts for its scant commercial exploitation.

Analogues of actidione that bear imide groups[141,143] have been synthesized with the object of eliminating toxic properties while maintaining repellent activity. Although glutarimide was found to be inactive, several phthalimides, in particular *N*-n-butylphthalimide[141] were found effective in deterring rodent attacks.

[154] J. R. Tigner and J. F. Besser, *J. Agric. Food Chem.*, 1962, **10**, 484.
[155] J. R. Tigner, *J. Wildlife Management*, 1966, **30**, 180.
[156] R. Traub, J. B. Dewitt, J. F. Welch, and D. Newman, *J. Amer. Pharm. Assoc.*, 1950, **39**, 552.



(24)

Malathion, *S*-(1,2-dicarbethoxyethyl)-*OO*-dimethyl dithiophosphate (24), exhibits a high degree of rodent-repellent action. Laboratory tests in India showed[157] that food sacks stored in a warehouse could be made resistant to attacks by *R. rattus* for considerable periods using a mixture of malathion and eugenol. Malathion presents a useful bonus since it is also an efficient insecticide, *e.g.* in the control of weevils on stored grain, while being non-toxic to poultry.[158]

Useful repellent activity against *M. musculus* with triphenyltin chloride or tributyltin chloride has been described.[159] Muslin treated with tributyltin acetate and protected by polyethylene films in the form of bags and tarpaulins gave short-term protection.[155] Envelopes made from polyethylene to which tributyltin chloride had been added prior to extrusion were found[160] to retard attacks from rats and mice. Use of tricyclohexyltin hydroxide has been claimed[161] to repel *R. norvegicus* from corrugated paper and expanded polystyrene boards, *etc.* The corresponding chloride and bis(tricyclohexyltin) oxide are also claimed[161] to possess rodent repellency.

The odours associated with predators are supposedly able to repel their prey. n-Butyl mercaptan (skunk odour) has been investigated[162] for its ability to repel rats. In one study, honey containing the repellant protected commercial feedstuffs stored on a farm. Pentachlorobenzyl mercaptan and mercaptides have been claimed[163,164] to be satisfactory rodent repellants.

C. Cables and Wiring.—Important cable and electrical-wiring systems are vulnerable to damage by rodents. Cables situated above the ground can be periodically inspected for damage but it is impracticable frequently to check underground cables which need to remain immune to rodent attacks. Repellent substances may either be incorporated into the cable, *etc.* or may be applied as a coating, or alternatively they may be dispersed in the soil surrounding the underground cable. Rodent damage to rope, twine, *etc.* has also demanded efficient counter-measures, in which repellants can play a part.

[157] S. K. Majumder, M. K. Krishnakumari, and J. K. Krishna-Rao. *Current Sci.*, 1964, **33**, 212.
[158] M. W. McDonald, J. F. Dillon, and D. Stewart, *Austral. Vet. J.*, 1964, **40**, 358.
[159] R. J. Zedler and C. B. Beiter, *Soap*, 1962, **38**, 75.
[160] E. E. Kimmel, U.S.P. 3 132 992 (*Chem. Abs.*, 1964, **61**, 7642*a*).
[161] E. E. Kenaga, U.S.P. 3 389 048 (*Chem. Abs.*, 1968, **69**, 43 042*g*).
[162] L. A. Ford and D. F. Clausen, *Chem. Eng. News*, 1941, **19**, 783.
[163] H. J. Miller, U.S.P. 3 139 379, (*Chem. Abs.*, 1964, **61**, 6314*e*).
[164] F. E. Lawlor and I. C. Popoff, U.S.P. 3 217 021 (*Chem. Abs.*, 1966, **65**, 8825*e*).

(25)

R55, *NN*-dimethyl-*S*-t-butyl-sulphenyl-dithiocarbamate (25), and similar types of compound are effective rodent repellants.[165,166] Pocket gopher damage to buried telephone cables has been restricted[167] by treating the surrounding soil with R55. When formulated in a cable-coating, this chemical produces a convenient barrier to rodent damage.[168]

A number of repellant formulations based on tributyltin salts are of interest for protection of cables and wiring. 'Bio Met 12',[169] when formulated in a plastic coating, is an effective repellant which has no adverse effects on other cable properties. Coatings based on tributyltin chloride in chlorinated rubber have been applied to telephone wires to increase their rodent resistance.[170]

Long-chain aliphatic amines and salts have been claimed[171] to prevent damage by rats to binder twine. Dodecylamine acetate has been suggested[172] as an effective means of protecting cordage and insulated wires against rodent attacks. Cord or twine treated with quinaldine and naphthenic acid was reported[173] to show rodent repellence.

9 Resistance to Rodenticides (Warfarin Resistance)

There are two kinds of resistance that may develop from the use of rodenticides.[38] The first type is an acquired tolerance to a poison that builds up in the rodent pest during treatment and is not passed from parent to offspring. This acquired resistance may arise from the use of acute poisons, and such instances have been referred to under the individual acute poisons. A more recently encountered type of resistance may appear after frequent use of anticoagulant poisons, *e.g.* warfarin. It is this latter resistance which can pass from one generation to the next that poses the more serious problem.

A. Introduction.—The physiological mechanism of the action of anticoagulants on the clotting capacity of blood and the role which Vitamin K plays in this process are rather involved and are still open to conjecture. It is nevertheless certain that Vitamin K and the anticoagulants act through the same mechanism

[165] L. D. Goodhue, U.S.P. 2 862 850 (*Chem. Abs.*, 1959, **53**, P6520*c*).
[166] W. R. Eddy, U.S.P. 3 503 800 (*Chem. Abs.*, 1970, **72**, 122 551*n*).
[167] T. H. Mailen and R. E. Stansbury, 15th Annual Wire and Cable Symposium, New Jersey, 1966.
[168] J. A. Shotton, U.S.P. 3 434 995, (*Chem. Abs.*, 1969, **70**, 107 255*j*).
[169] Anon. *Chem. Eng. News*, 1967, **45**, 24.
[170] 'Rodent Resistant Cable Materials', U.S. Army Applied Entomology Group Tech. Report No. 3, 1968.
[171] P. Jucaitis, U.S.P. 2 868 674 (*Chem. Abs.*, 1959, **53**, 13 500*a*).
[172] J. P. Barrett and E. W. Segebrecht, U.S.P. 2 822 296 (*Chem. Abs.*, 1959, **53**, 1 626*i*).
[173] P. Jucaitis, U.S.P. 2 864 727 (*Chem. Abs.*, 1959, **53**, 6520*d*).

and therefore are mutually antagonistic.[1,174] Vitamin K is vital to the complex blood-clotting scheme of an animal, so that any antagonism shown towards this vitamin could have lethal results. The administration of warfarin therefore interferes with the normal clotting of blood and may further hasten the onset of internal bleeding by causing a breakdown of blood vessels.[175] The discovery that, on occasions, warfarin and other anticoagulants lose their toxic action to wild rodents has been the subject of much concern.

B. Discovery.—The first case of resistance to warfarin in wild animals was discovered[176] in 1958 near Glasgow where populations of *R. norvegicus* were not effectively controlled by anticoagulants. Two years later, an area roughly centred on Welshpool on the English–Welsh border, was also found[175] to contain *R. norvegicus* infestations similarly resistant. Since that time small areas in Kent, Somerset, Gloucestershire, Berkshire, Nottinghamshire and Carmarthenshire have been found[177] to harbour resistant rats as well as places in Denmark,[178] Hungary,[179] and the Netherlands.[180] Other rat species, *Holochilus sciureus* (British Guiana)[26] and *Bandicota bengalensis* (Ceylon)[177] have been reported to contain anticoagulant-resistant members.

In some ways a more serious threat has been recognized in the U.K. by the discovery that many populations of *M. musculus* have the inborn ability to tolerate anticoagulants.[181,182]

C. Resistance Mechanism.—A vigorous programme of research was mounted in several laboratories[177,183] when resistance had been confirmed. The results of studies on susceptible and normal rats indicated that the genetic pattern in each resistant population could well be different. It was elucidated that although a single gene was responsible in both the Welsh and Scottish areas, it was possibly a different one in each case. The single-gene basis for the resistance accounts for the rapid spread of inherited resistance,[177] which was far more rapid than would be expected if several genes were involved. The pattern of resistance in other groups is more complicated, *e.g.* in Denmark, tests with resistant wild rats showed that no acceptable theory could explain their genetic background.[184] The position is again complicated with resistant *M. musculus*,[185] for resistance

[174] I. H. Stockley, *Pharm. J.*, 1970, **205**, 167.
[175] D. Drummond, *New Scientist*, 1966, **30**, 771.
[176] C. M. Boyle, *Nature*, 1960, **188**, 517.
[177] J. H. Greaves, *Agriculture*, 1970, **77**, 107.
[178] M. Lund, *Nature*, 1964, **203**, 778.
[179] W. B. Jackson, *Pest Control*, 1969, **37**, 51.
[180] A. J. Ophof and D. W. Langeveld, 'Rattenbiologie und Rattenbekämpfung', ed. K. Becker, G. F. Verlag, Stuttgart, 1969, p. 39.
[181] E. W. Bentley, Ref. 180, p. 19.
[182] P. B. Cornwell, *Municipal Engineering*, 1966, **143**, 2371.
[183] J. G. Pool, R. A. O'Reilly, L. J. Schneider, and M. Alexander, *Amer. J. Physiol.*, 1968, **215**, 627.
[184] M. Lund, Ref. 180, p. 27.
[185] F. P. Rowe and R. Redfern, *J. Hyg. (Cambridge)*, 1965, **63**, 417.

may be either under polygenic control or controlled by a single gene influenced by modifiers.

D. Treatment.—Initial observations revealed that, as expected, areas containing resistant rats had soon begun to spread. Therefore, the first practical measures introduced were based on containment, to allow eradication procedures to be more effective. In 1966, in the Welsh area an operation was introduced by the Ministry of Agriculture, Fisheries, and Food in which a cordon, approximately three miles wide, was set up around the known perimeter of the resistance area.[175] All farms in this perimeter zone were inspected by Ministry operators and systematically treated with acute rodenticides to create a virtual 'rat-free' zone.

Eradication procedures soon indicated that all the better-known anticoagulants were of little value since resistance was shown to both coumarin and indanedione compounds alike. A short-lived hope that one anticoagulant could stem the tide was dismissed when coumatetralyl-resistant animals were discovered.[181] No toxic effects were introduced by these anticoagulants; this was suitably demonstrated when anticoagulant-formulated bait-materials afforded useful prebaits for acute poisons.[186] The return to acute poisons, together with the supplementary techniques of fumigation and trapping, proved quite adequate, if not convenient, to keep infestations down to tolerable levels.

The Welsh containment operation was discontinued in 1969 as monitoring areas outside the zone indicated the existence of resistant rats.[177] Conspiring against the success of this scheme were the reluctance of farmers in the area to stop using warfarin and other anticoagulants and the severe epidemic of Foot and Mouth disease which prevented the free movement of Ministry operators.

E. Present Situation.—Although the Welsh cordon experiment was apparently unsuccessful, useful information had accrued during the study which showed that the situation was not as desperate as had been widely reported, for:

(*a*) There is basically no abnormal movement of resistant rats although the area of resistance is gradually increasing.

(*b*) Numbers of resistant rats in particular areas seem to have reached a plateau level. The discovery that resistant rats require[187] more Vitamin K suggested that these rats had the lowest survival potential. Thus if the use of anticoagulants ceased, the numbers of resistant rats should decrease.[177]

(*c*) The numbers of rats existing currently in infested areas are of the same order as those that existed in these areas before the outbreak of resistance; consequently there is no increase in the spread of rat-borne diseases.[188]

The treatment of resistant mice, although less publicized, is still a problem, for resistant infestations are on the increase. In dwellings particularly, the use

[186] F. P. Rowe and B. Rennison, personal communication.
[187] M. A. Hermodson, J. W. Suttie, and K. P. Link, *Fed. Proc.*, 1969, **28**, 386.
[188] Anon., *Lancet*, 1970, 987.

of acute poisons is limited because of potential hazards of toxicity to man and non-pest species.

10 Future Outlook

Research is under way to discover new rodenticides with different modes of action to replace many unsatisfactory poisons commonly in use. In this connection the Ministry of Agriculture, Fisheries, and Food in the U.K. have given a high priority to testing of candidate rodenticides.[177,189] A request for the co-operation of chemical industry to make available compounds previously considered of little value owing to toxicity has been made by the Ministry. Progress is also being made[190] in the further understanding of anticoagulant resistance.

Since long-term approaches to rodent control might include selective chemosterilants, the search for suitable substances is similarly at the outset a chemical problem.

Further studies of rodent behaviour would benefit control, especially with regard to repellants and attractants which could be valuable in directing the movement of rodents to baiting areas. Improved baits subjected to new formulation procedures, *e.g.* microencapsulation,[64,191] would be an additional aid, for it has been suggested[32] that 'not so much specific poisons but baits that are only attractive to the pest species' is the requirement for poison baiting.

However, in many cases, if improved standards of hygiene together with rodent proofing and removal of food and cover were introduced, the number of rodents would decrease naturally through environmental pressures.

The author wishes to thank staff of the Pest Infestation Control Laboratory, Ministry of Agriculture, Fisheries, and Food, for helpful discussions. The time allowed for the preparation of this article at the Lilly Research Centre is gratefully acknowledged.

[189] F. P. Rowe, J. H. Greaves, R. Redfern, and A. D. Martin, Ref. 15, p. 126.
[190] J. H. Greaves and P. Ayres, *Nature*, 1969, **224**, 284.
[191] J. H. Greaves, F. P. Rowe, R. Redfern, and P. Ayres, *Nature*, 1968, **219**, 402.