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THE PROSPECTS AND ASSOCIATED CHALLENGES FOR THE BIOLOGICAL CONTROL OF RODENTS

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ABSTRACT: Biological control using macro- or micro-parasites is a promising research area for control of rodents. The largest impediment to progress is a dearth of high quality research, under field conditions, on wild rodents and their diseases. A major challenge is to identify a candidate control agent which is sufficiently pathogenic, has a high transmission rate and is target specific. Once this has been done, ecological studies of both the host and the disease agent, and of the epidemiology of transmission, are required. Whether the desired pathogenicity is via increased mortality and/or reduced fertility will depend on the agent and on the dynamics of the pest species in particular agricultural systems. Overall, the best prospects for the biological control of rodents lies with agents that reduce fertility rather than increase mortality. The development of immuno-contraception using a virus as a vector is proffered as the most promising generic approach for the biological control of rodent pests.

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INTRODUCTION

Biological control has been defined as the action of biological organisms to maintain another organism at a lower average density than it would attain in their absence (Waterhouse and Norris 1987). Operatively this is a sufficient definition, however, from a wildlife management viewpoint a biological control agent would only be successful if the pest organism is maintained below a defined density. This density is generally related to the "economic injury level" of a grain farmer, forester, grazier, etc. If the damage by a pest species is below this level then the species is tolerated and further control is not required.

In a world where the current emphasis is on conserving or enhancing the quality of the environment, scientists at CSIRO, Division of Wildlife and Ecology, are concentrating on biological agents in their efforts to control vertebrate pests of agricultural, urban and "natural" landscapes in Australia. If successful, biocontrol will lead to less reliance on chemicals, be environmentally benign, and could also be more costeffective than current chemical control methods. Such considerations are of immense importance not only to developed countries but also to developing countries that have perennial rat problems in staple crops such as fice.

Interest in the potential of biological agents to regulate or limit vertebrate populations was sparked in the late 1970s when theoretical models indicated that microviruses, bacteria and protozoans) and macro- (helminths and arthropods) parasites could regulate host populations (see Anderson 1980 for review). This increased interest was accompanied by a more positive attitude to the potential of biological agents to control vertebrate pest species, as attested in a series of reviews on the potential of parasites (Scott and Dobson 1989, Spratt 1990, Singleton and Redhead 1990b), predators (Sinclair 1989, Pech et al. 1992) and both parasites and predators (Wood 1985) to regulate vertebrate (generally pest) populations.

The recent interest in the role predators play in regulating or limiting field populations of prey species clearly underlines that biological control is not restricted to the use of disease agents. Whilst recognizing that some of the non-disease approaches to controlling mammalian pests have potential (see Wood 1985 for a broader appraisal), in this paper I will restrict my consideration of biological control to the potential use of micro- and macro-parasites. Moreover, I will be confining my focus to the prospects of using these agents to control pest species of rodents.

RODENTS - A HISTORIC CHALLENGE THAT KNOWS FEW BOUNDARIES

"The rate of propagation of field mice in country places, and the destruction that they cause, are beyond all telling" (Aristotle 384-322 B.C., *in* Thompson 1910, p 5806).

"The mice are now invading the houses of the mallee district... from 1,000 to 1,500 dead mice is not out of the way for a night's poisoning. The mice go for everything eatable...gnawing at harness, clothes, bedding, or anything else that takes their fancy" (Melbourne Argus, Australia, April 1917).

"Although damage at 10% (by rats at the district level) may not sound alarming it becomes disastrous if all the rice in one village is completely damaged. I have personally been in such villages...in the Viengkam district. Some farmers visited have not had a rice harvest for two successive years." (Walter Roder, 1993 - Lao/IRRI Project, Laos, personal communication)

These quotes encapsulate the severity and magnitude of the problems caused by mice and rats. First, rodents are an age old problem; these quotes could have been interchanged (or applied the date 1993 to the Australian quote) and lost nothing in their relevance to a particular time or country. Second, rodents have no regard for international boundaries. Third, the severity of a rodent problem cannot be simply related to socio-economic status; both developed and developing countries experience the full effects of chronic and/or acute rodent problems. Finally, rodents are a problem in virtually every major climatic zone. The above examples cover tropical and mediterranean climates but other examples could have been provided for such extremes as true deserts (e.g., Simpson desert, Newsome and Corbett 1975) or sub-antarctic islands (e.g., Marion Island and Macquarie Island).

The challenge is not only to be able to manage rodent problems on a local or global scale, but also to be able to provide an ecologically sustainable method of management. Biological control using disease agents offers an attractive avenue to achieve such a challenge. The remainder of this paper will consider some of the exciting prospects in this field and some of the challenges faced in trying to transform the potential into reality.

I wish to point out that I do not view biological control and chemical control as being mutually exclusive. The aim is to reduce our reliance on chemicals and the encumbered risk they pose to wildlife and to humans. If a biological agent alone is unable to provide effective management of rodents but has an additive or synergistic effect when used in conjunction with chemicals, then provided chemical usage is reduced, this aim will be achieved.

BIOLOGICAL CONTROL - A MODEL SYSTEM

Theoretical models suggest that micro- and macroparasites may regulate mammalian host populations under certain circumstances (e.g., Anderson and May 1978, McCallum and Singleton 1989). There have been numerous successful biological control programs instigated against plants and insects. In vertebrate populations, however, the only successful control program has been the use of the myxoma virus against rabbits in Australia (see Fenner and Myers 1978, Fenner 1983, for details). Interestingly the success of myxoma was due to its effect on the mortality of rabbits. By comparison, a recent study which modelled the relative impact of disease on host populations showed that microparasites have the greatest impact if they reduce fertility but do not affect host mortality. The findings for macroparasites were more complex but intermediate pathogenicity produced the greatest reduction in host density (McCallum 1994).

The dearth of successful biological control programs of vertebrate pests relates largely to the lack of effort by researchers rather than to it being an insurmountable or fruitless task. This lack of effort is due in some part to disease not being in vogue during the 1950s, 1960s and 1970s as an important factor limiting vertebrate populations and to the number of failed introductions of vertebrate predators to control pests, which in many cases led to additional biological problems (see Spratt 1990 for details). Other factors behind the lack of recent research effort include the difficulty to detect the impact of a micro- or macro-parasite on a population (see McCallum 1994), the failure of early attempts using bacterial agents because of non-target infections (including humans), the lack of host specificity of many micro- and macroparasites, and the long-term nature of the research. Together, this has led to a widely accepted view that parasites are not important in regulating mammalian populations, despite few comprehensive field studies with data to support either viewpoint (see Scott and Dobson

1989, Singleton and Redhead 1990b, Spratt 1990 for reviews).

A recent series of laboratory experiments on the dynamics of a mouse-nematode interaction have vindicated the conclusions drawn from the mathematical models, at least for macro-parasites (Scott 1987, 1990). Unfortunately, the modelling and laboratory studies are a long way ahead of field studies. Some small scale enclosure experiments have been conducted on wild rodent populations (Barker et al. 1991, Gregory 1991) and a large scale replicated and manipulative field trial is in progress examining the effect of a liver nematode, *Capillaria hepatica*, on field populations of house mice, *Mas domesticus*, in Australia (Singleton et al. 1994).

STRATEGIES FOR BIOLOGICAL CONTROL

Strategies to manage rodent populations can concentrate on one or more of three basic demographic parameters: death rate, birth rate and dispersal (see Singleton & Redhead 1990b). Rodent pest species characteristically have a moderate to low survival rate, high reproductive rate (relatively large litter sizes and early onset of sexual maturation) and a social structure which promotes dispersal of young animals. Rodents also are typically opportunistic breeders and are able to rapidly take advantage of an extension in suitable conditions for breeding (e.g., the change in production from one to two rice crops per year resulted in the rice field rat, Rattus argentiventer, changing from one to two breeding seasons per year, Lam 1980). Together, these life history traits enable the species to take rapid advantage of changes in the availability of key resources. This is particularly noticeable in unstable habitats such as agricultural landscapes, where vast areas of cropped land can literally change overnight from sub-optimal to optimal habitat for rodents.

Mortality Increasing Agents

<u>Micro-parasites</u>. The classical approach deployed to control insects is to increase mortality. With rodents, this approach dates back to unsuccessful attempts to control them using bacteria in Russia and Europe earlier this century (Elton 1942, Bykovskii and Kandybin 1988).

Interest in the potential of using biological agents to control rodent populations through increasing mortality is slowly gaining momentum. For example, in Southeast Asia there is strong interest in Thailand and Vietnam in the prospect for the biological control of rodent pests. Both countries have some research in progress but it is at a very early stage (T. Jakel personal communication 1993, Pham Van Toan personal communication 1993). In Vietnam, the candidate is a zoonotic bacteria, Salmonella enteriditis. The potential for widespread use of this organism for controlling rodent pests in agricultural crops, therefore, is limited. In Thailand, they are examining the effectiveness of a protozoan, Sarcocystis singaporensis, for controlling the ricefield rat, R. argentiventer. This research is at a very early stage. Because rats are an intermediate host of the protozoan, there will be time delays in transmission to other rats, and the rate of transmission will be dependent on the density of the definitive hosts. The definitive hosts are mainly snakes, which are generally at low densities in intensive

agricultural regions of Southeast Asia. Thus, the rate of transmission is likely to be low and therefore the protozoan is more likely to function as a bio-cide (a biological agent that is presented in a bait to kill animals rather than relying on natural transmission).

For *Sarcocystis* to be used successfully as a bio-cide it must satisfy two primary conditions. First, it needs to be highly pathogenic to rats under field situations. Second, cost of production and distribution of the parasite will need to be competitive compared to existing chemical rodenticides. If the first condition is met and not the second, then the adoption rate by Thai farmers who generally have very little disposable income, is likely to be low.

The "typical" life history pattern for pest species of rodent outlined in the previous section, underlines an important pitfall for methods of increasing the death rate of rodent pests. If the death rate is not sufficiently high, in every likelihood there will be compensatory increases in survival and reproduction. Also, if the area over which control is implemented is not sufficiently large (thousands of hectares for mice in Australia) then reinvasion will occur rapidly (Twigg et al. 1991). The use of disease to increase mortality will need to have either a high kill rate coupled with a high transmission rate, or act at a critical time in the life history of the rodent population, such as just prior to the main breeding season. The former is an unlikely combination because disease agents such as viruses which have high kill rates, usually produce epidemics which are acute and self limiting (e.g., parvovirus in mice). Another limiting factor with diseases that increase mortality is that there will be rapid selection for genetically determined resistance by the host or for reduced virulence (and hence increased persistence) in strains of the disease. Both situations occurred following the release of myxoma virus in rabbits in Australia (Fenner 1983).

Epidemiological knowledge of an infectious organism, its method of transmission and its persistence in the environment, is required to ascertain the prospects for biological control of rodents using agents which increase mortality. This then requires consideration within the context of the social structure and population dynamics of the host.

In the case of micro-parasites of rodents, most of our knowledge of modes of transmission, persistence, clinical effects, etc., is confined to laboratory colonies of mice and rats. Indeed, this store of knowledge is large (see Foster et al. 1982, Bhatt et al. 1986). However, virtually nothing is known about ecological and epidemiological aspects of these viruses in the wild. Our knowledge base is restricted to a couple of surveys (Kaplan et al. 1980, Smith et al. 1993) and two longitudinal studies (Descoteaux and Mihok 1986, Singleton et al. 1993) of changes in the seroprevalence of murine viruses. It is disappointing that so few studies have been conducted on rodents because these are an important first step. To highlight what can be gained from such studies, the major findings from the two Australian studies of murine viruses in wild mice will be considered next.

Eight of fourteen viruses screened were recorded in the first study and six occurred at most of the fourteen sites in southern and eastern Australia where the mice were trapped (Smith et al. 1993). The mouse populations at these sites were at different densities. It appeared that viral epidemics occurred among high density mouse populations just prior to a precipitous decline in host density. A subsequent 13 month study of wild mice at one of these sites concentrated serological work on the six most common viruses recorded in the survey study (Singleton et al. 1993). The density of the mouse population varied considerably throughout this time. Mice were seropositive to all six viruses during the study and the seroprevalences of five of the viruses were density dependent. During a period of rapid decline in host density, the seroprevalence of two of the viruses, minute virus of mice (MVM) and reovirus 3 (reo 3), increased significantly. The seroprevalences of these two viruses were inversely related to host survival. Combined with their density dependent changes in seroprevalence, this indicated that MVM and reo 3 may play an important role in regulating mouse populations. Another study of the dynamics of the seroprevalence of these six murine viruses has just been completed in Australia in a very different agricultural landscape some 1,000 km north-east of the first study (G. R. Singleton unpublished data). The study was conducted over three years during a build up, peak and decline in mouse densities. The results were similar to the previous findings with the seroprevalence of MVM and reo 3 inversely related to host survival.

A limitation of the above studies is that seroprevalence provides only a history of what has happened not what is happening at the time of sampling. The question that begs itself is whether MVM and/or reo 3 could be used strategically to control mouse populations. Nevertheless, basic studies of both viruses straddling the interface of laboratory virology and field ecology are required. This is an unusual mix in rodent biology that needs to be blended if further headway is to be made. Progress will be slow because of the nature of the research, but at the same time extremely rewarding if the potential of viruses as biological control agents can be adequately assessed.

Theoretical models indicate that a microparasite at high prevalence within a population is unlikely to be having a major effect on the size of that population (Anderson 1979). However, because so little is known about the effect of murine viruses on rodents under field conditions, we need to be careful in assuming that those viruses which cause epizootics and show density dependent effects are the best ones to concentrate upon. Viruses which have consistently high seroprevalences may play an important role either by themselves or in tandem with other viruses. One of these is murine cytomegalovirus which has the interesting properties of causing immuno-suppression in mice under certain conditions (e.g., nutritional stress, Teo et al. 1991) and of being able to enter a latent phase and recrudesce when an animal is under stress.

Further research is required on the decision rules following basic seroprevalence studies on murine viruses with regard to identifying which viruses have the best prospect for limiting populations of their rodent host below the levels that cause economic and social hardship. <u>Macro-parasites</u>. There are few studies under field conditions on the effect of macro-parasites on rodent mortality. The results are generally not encouraging from the point of view of using them as prospective biological control agents (e.g., Singleton 1985).

An elegant series of laboratory experiments on the effects of the nematode, Heligmosomoid.es polygyrus, on the dynamics of laboratory colonies of mice provide strong evidence that this parasite can regulate mouse abundance in the absence of other possible regulating agents (Scott 1987, Scott 1990). However, these experiments were conducted under ideal conditions for transmission of the parasite and on laboratory mice. A subsequent study examined the interaction between H. polygyrus and wood mice (Apodemus sylvaticus) in outdoor enclosures. Although the rate of population growth and effects on survival were lower than that reported by Scott (1987), the parasite had a significant impact on the survival of wood mice (Gregory 1991). In Australia this parasite appears to be restricted to habitats of high moisture content in the southeast of the continent (Singleton 1985, G.R. Singleton unpublished data). Mouse plagues occur in this region on average one year in seven (Singleton and Redhead 1990a). It would be interesting to examine whether this parasite plays a role in regulating mouse populations in non-plague years.

Fertility Reducing Agents - Natural

The highly fecund nature of pest species of rodents indicates that efforts to reduce fertility rather than mortality may be a more effective management strategy. There is theoretical support for this approach to managing vertebrate pest species (e.g., McCallum and Singleton 1989, Caughley et al. 1992). Again, there are few well designed field studies aimed at examining this concept.

The potential of using fertility control as a management option for rodents is exemplified in Australia. Mouse (M. domesticus) populations in the cereal-growing regions in Australia have larger average litter sizes 12-18 months prior to a plague than at other times (Singleton and Redhead 1990a). Also, in the mallee wheatlands at least, there is much variation in which months mice begin and cease breeding; the length of the breeding season is longest 12 months prior to a plague (Singleton 1989). If mouse populations are prevented from having these occasional seasons of high productivity, then perhaps plagues would not occur. Modeling of mouse population dynamics supports this contention; either maintaining the average litter size below five or reducing the frequency of litters produced per female appears to be sufficient to prevent plagues developing (Redhead 1987). Our understanding of mouse population dynamics has enabled these targets of fertility reduction to be set. The challenge is to find the means to achieve what appear to be attainable targets.

<u>Microparasites</u>. I am not aware of any studies which have focussed on using naturally occurring micro-parasites to manage rodent populations through reducing their fertility.

<u>Macro-parasites</u>. A hepatic parasite, *Capillaria hepatica*, significantly reduced the productivity of laboratory female mice through reducing the number of litters produced and the number of young weaned over three months (Singleton and Spratt 1986). Based on these data and knowledge of life history parameters of both mice and C. hepatica, models were developed of the likely interaction between the parasite and mice. The modeling indicated that the parasite's effect on productivity would be sufficient for it to regulate the host population below plague densities (McCallum & Singleton 1989). These results formed the basis for a multidisciplinary research program into the potential of C. hepatica to control mouse plagues. Our progress and the potential for success have been reviewed elsewhere (Singleton and McCallum 1990, Spratt 1990). Currently, the effectiveness of the parasite is being assessed by a series of replicated and manipulative field studies (Singleton et al. 1994).

A laboratory study of similar design to Singleton and Spratt (1986) assessed the effect of a cestode (Vampirolepis straminea) on wild mice (M. domesticus) trapped from the northern part of the south island of New Zealand. Marginal effects on reproduction were reported but the author concluded that the parasite was probably not suitable as a biological control agent of mice (Murphy 1991).

Fertility Reducing Agents - Recombinant Viruses

Recent advances in molecular biology and reproductive physiology have provided a new focus: blocking of fertilization through an immunological response to proteins involved in an animals own reproduction. Immuno-contraception falls within the definition of biological control stated in the introduction when biological organisms are being used as carriers (vectors) of these immunogens.

Micro-parasites. Fertility methods that use chemo-sterilants or steroids or use agents to block gonadal regulation hormone (GnRH), affect the normal hormonal function of reproductive organs and treated animals become socially subordinate (see Marsh 1988, Bomford 1990, Tvndale-Biscoe 1993 for discussion). In pest species with a high reproductive potential the lost output of these animals would rapidly be compensated by unaffected, socially-dominant animals. Another approach is to induce sterility from an immunological reaction to proteins of sperm (e.g., structural proteins) or ova (e.g., zona pellucida) (Aitken and Paterson 1988). Sterility is produced through blocking fertilization or implantation of the ova. In either case there would be no interference with the steroidal functions of the animal's gonads. Thus, a sterilized animal should be able to maintain its social status.

Once an immuno-contraceptive agent is developed the next challenge is to sterilize a sufficient proportion of a population to enable effective management. Delivery of the agent may be by baits or by a species-specific disseminating recombinant pathogen.

The Centre for Biological Control of Vertebrate Pest Populations, with its headquarters at CSIRO Division of Wildlife & Ecology, is involved in research on immunocontraception of vertebrate pests and methods of delivery of a sterilizing agent. The concept and progress of the research is reviewed by Tyndale-Biscoe (1993). Although the current focus of the centre is on the biological control of rabbits and foxes, much of the basic research supporting the potential of this approach was on laboratory rodents. For example, sperm antigens (Shagli et al. 1990) and zona pellucida peptide (Millar et al. 1989) have been shown to cause contraception in rats and in mice. This work on rodents has been restricted to the laboratory but has great potential for use in managing rodent pests.

The potential of immuno-contraception as a method to manage rodent pests is reviewed elsewhere (Singleton and Redhead 1990b, Shellam 1994). The essential and desirable characteristics of a virus best suited to act as a vector of a fertility blocking agent in rodents are listed in Table 1. This research holds much promise as a generic approach for the biological control of rodent pest species.

The major criticism of the immuno-contraceptive approach is that it is dependent on the release of a genetically engineered micro-organism. The legal and ethical issues associated with viral vectored immunocontraception have not been ignored by its proponents (see Tyndale-Biscoe 1993). Specific minimum safe-guards such as a species-specific virus and sterilizing agent form an essential part of the control strategy. However, regardless of the built-in checks in the system, ultimately it will be the public who will have to address the risks and benefits of this approach to wildlife management.

CONCLUSION

There are two main conclusions from this review. First, the best prospects for the biological control of rodents lies with agents that reduce fertility rather than increase mortality. Second, the most promising generic approach is immuno-contraception using a pathogen as a vector. These conclusions are consistent with findings from theoretical modelling of the interaction between disease and vertebrate hosts (Anderson 1979, McCallum 1994).

Table 1. Essential and desirable properties for a virus which will act as a carrier of an immuno-contraception agent for the biological control of rodents (after Shellam 1994).

Essential Properties	Desirable Properties
Species specific and natural infects target species.	Virus is already present in the country.
Readily transmitted in target species.	Virus establishes persistent and latent infection.
Insertion of foreign gene is stable and does not affect viral growth or transmission.	Good local IgA response which does not interfere with transmission.
Stimulates long lived immune response and immunological memory.	Recombinant virus can be introduced and maintained in the presence of existing immunity.
Panel of isolates available. Epidemiology of infection and transmission understood and site of viral growth known. Approval by regulatory authorities likely.	Mechanism for any genetically determined host resistance is known.
	Genetically determined host resistance does not interfere with infection or transmission.
	Mechanism of transmission known.
	Does not cause lethal infection.
	Virus is sexually transmitted.
	Knowledge of the epidemiology of infection and transmission of natural virus variants.
	A DNA rather than a RNA virus because they have greater genetic stability.

Overall, the prospects for biological control of rodents are much more promising now than they have ever been. Although a dearth of appropriate high quality research is still the largest impediment to progress, there has been a noticeable increase of interest over the last decade in the role of micro- and macro-parasites in the regulation or limitation of field populations of mammals. For rodents, we need to channel this interest into the basic population biology of both host and pathogen, and the associated epidemiology of the interaction between them. This underlines the necessary prerequisites for success: a good understanding of the ecology of both the pest species and the disease agent, and development of a well managed inter-disciplinary program of collaborative research.

The most important challenge is determining what disease agents occur naturally in rodent populations, the most difficult decision is choosing the disease agent to study. A good starting point is a survey of potential pathogens of key rodent pests along the lines of the geographical (Smith et al 1993) and longitudinal studies (Singleton et al. 1993) conducted on house mice in Australia.

Finally, I have used our research on the interaction between mice and C. hepatica to clarify a number of points. Interestingly, this system is not ideal because of the likely disappearance of the parasite when the density of the host population is low. Therefore, the biological agent would have to be used in a tactical manner by releasing it in specific habitats during the formative stage of an outbreak of a mouse population (Singleton and McCallum 1990). This highlights a good point on which to end-in our consideration of the prospects of biological control agents we need to be flexible. If a particular disease agent does not have all the ideal characteristics (see Spratt 1990) do not discount its use without considering whether the particular rodent pest species causes an acute or chronic problem, the particular environmental system in which it needs to be managed and whether it can be used in conjunction with other pathogens or with chemical pesticides.

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