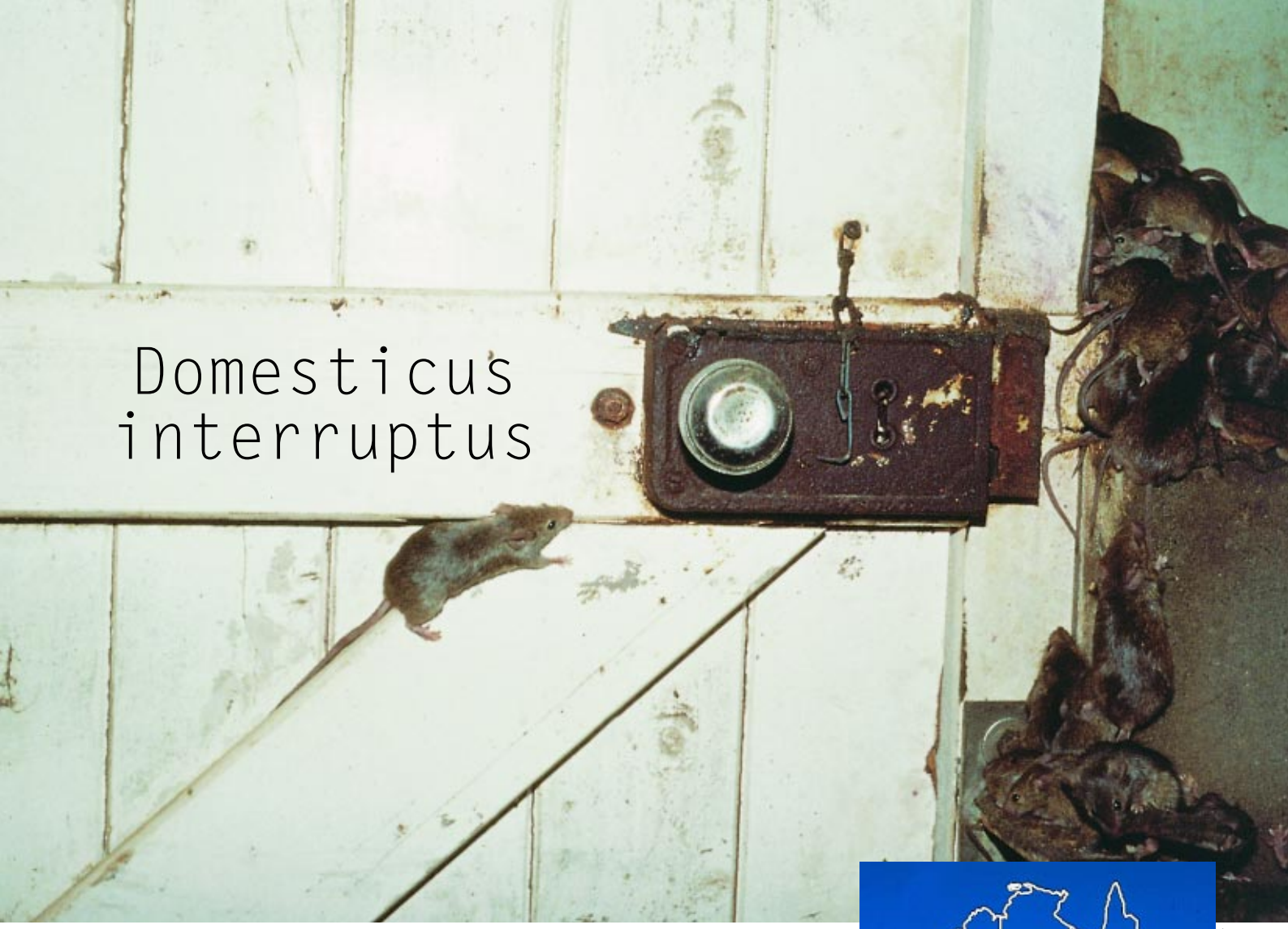
Domesticus interruptus

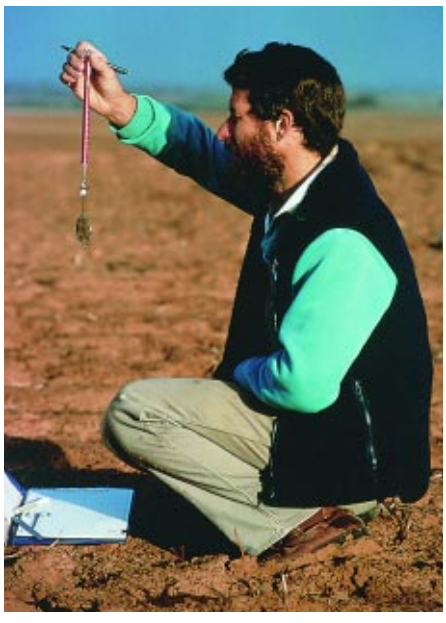


Researchers are applying their knowledge of immunology to develop a novel mouse contraceptive. **Steve Davidson** reports.

When the introduced house mouse 'goes bush' it becomes a formidable pest, despite its small size and meek nature. The trouble is the species has a remarkable capacity to multiply, exceeding even that of the rabbit. A female house mouse (*Mus domesticus*) can produce a litter every 21 days, so one pair of mice can theoretically give rise to more than 600 offspring in six months. Little wonder that, under the right conditions, mouse populations can quickly become plagues.

This is a real problem for farmers in the wheat-sheep belt of eastern and southern Australia who suffer severe grain losses during mouse plagues. Feral mice can reach population densities of more than 1000 per hectare during outbreaks and control using poisons is costly. For example, the bill for a single bait application to a 46 000-hectare property, during a 1993 mouse plague, was about $319 500. In the spring of 1999, in New South Wales alone, more than 500 000 hectares of farmland were aerially baited to control mice.

Recognising the need for a better way to control mouse numbers, scientists at Canberra's Pest Animal Control Co-operative Research Centre are tackling the pest's ability to multiply. Leader of the project, Dr Grant Singleton, says the technique, if successful, will complement, or possibly replace, traditional poisoning and trapping.



Photos: CSIRO Wildlife and Ecology

Right and above: Mice weigh in at only a few grams, but collectively have a dramatic impact when abundant.

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Signs of mice, from top to bottom.

Desperate measures – a 'mouse-proof' elevated haystack.

Cunning mice will dig up individual grains of sown wheat.

Mouse damage to maize and wheat.

The edges of this crop suffered mouse-damage after sowing.

So how do you stop mice breeding so fast? For a change, the method under investigation for mice follows an early experiment done on humans, rather than vice versa! In 1932, a paper in the *American Journal of Obstetrics and Gynaecology* reported that giving women injections of human spermatozoa prevented pregnancies for a full year. This was due to an immune response.

The mouse project is in the hands of Dr Malcolm Lawson and Megan Lloyd, of the University of Western Australia, and Dr Lyn Hinds, Dr Chris Hardy, Dr Ron Jackson, Jose ten Have and Lisa Farroway, of CSIRO. All are scientists of the CRC.

Sabotaging mouse fertility

The method under investigation uses the mouse's own immune system to prevent successful breeding. When the immune system of a mouse encounters cells or proteins in the bloodstream that come from the mouse reproductive system, it reacts as if these are life-threatening bacteria or foreign bodies, and neutralises them by means of protective antibodies. So by inoculating female mice with modified mouse reproductive cells of some kind, their immune response is primed to act against those antigens. When they next encounter them, fertilisation is blocked by the anti-sperm or anti-egg antibodies, and no pregnancy occurs. Scientists call this immuno-contraception; contraception through manipulation of the immune system.

'It is the perfect way to counter pests like mice that are highly fertile,' Hinds says. 'Relying on conventional control methods that kill mice is often futile against a pest that can recover by rapid breeding or immigration from untreated areas. Immuno-contraception should prove more humane and environmentally benign as well as cheaper and less labour intensive.'

Research by other scientists has indicated that sterilising individuals in a population of mammal pests actually has a greater effect than removing them. The beauty of immuno-contraception is that the sterile mice not only fail to breed, they also become something of a burden to the entire pest population in that they remain to compete for food and space. If they retain their social status, they could also continue to suppress the breeding of other subordinate mice.

Overall, fertility control is intended to slow population growth so that the pest does not exceed numbers at which economic damage is unacceptable, in this case, to grain growers. Total extermination is not the goal – indeed there is no loss of life!

Delivering the crucial antigen

So what is the best antigen to use? Will it cause infertility without other side effects? And how can it be delivered into mice on a broad scale? Clearly, not by injecting thousands of them, although this is the effect required.

Initial work at the CRC, by Dr Hugh Tyndale-Biscoe and Dr Mark Bradley, concentrated on sperm antigens to control mammal pests, but these proved disappointing and attention turned to antigens from the female gamete (the egg or oocyte). The outer coating of a mouse egg in the ovary (known as the zona pellucida) consists of three proteins: ZPA, ZPB and ZPC. The latter, ZPC, is the receptor for sperm when they bind to the egg during fertilisation and it was the first antigen tested by the scientists in mice. They reasoned that if female mice could be stimulated to produce an immune

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response to ZPC, the anti-ZPC antibodies attached to the mouse egg would make things difficult for egg-seeking sperm and hopefully block fertilisation.

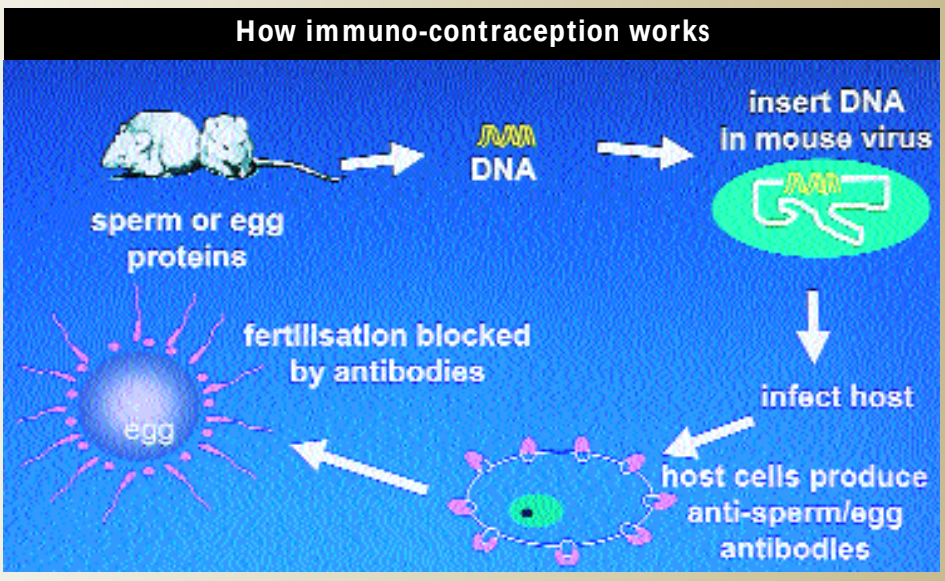
After looking at alternatives, the CRC scientists have decided to deliver the antigen in a virus known as murine cytomegalovirus or MCMV. It is an ideal delivery system, being naturally present in house mouse populations and highly species-specific. The virus is persistent, but not fatal, and spreads by close contact between mice. The idea is to insert genes for the mouse ZPC (from eggs) into the DNA of the virus, then let the virus do the work (see diagram).

As the virus spreads through the pest population, so should the antigen and hence the immuno-contraceptive effect. A proportion of the mouse population will be sterilised and population growth will be slowed. That is the theory. To date, results of laboratory and cage experiments have proved promising.

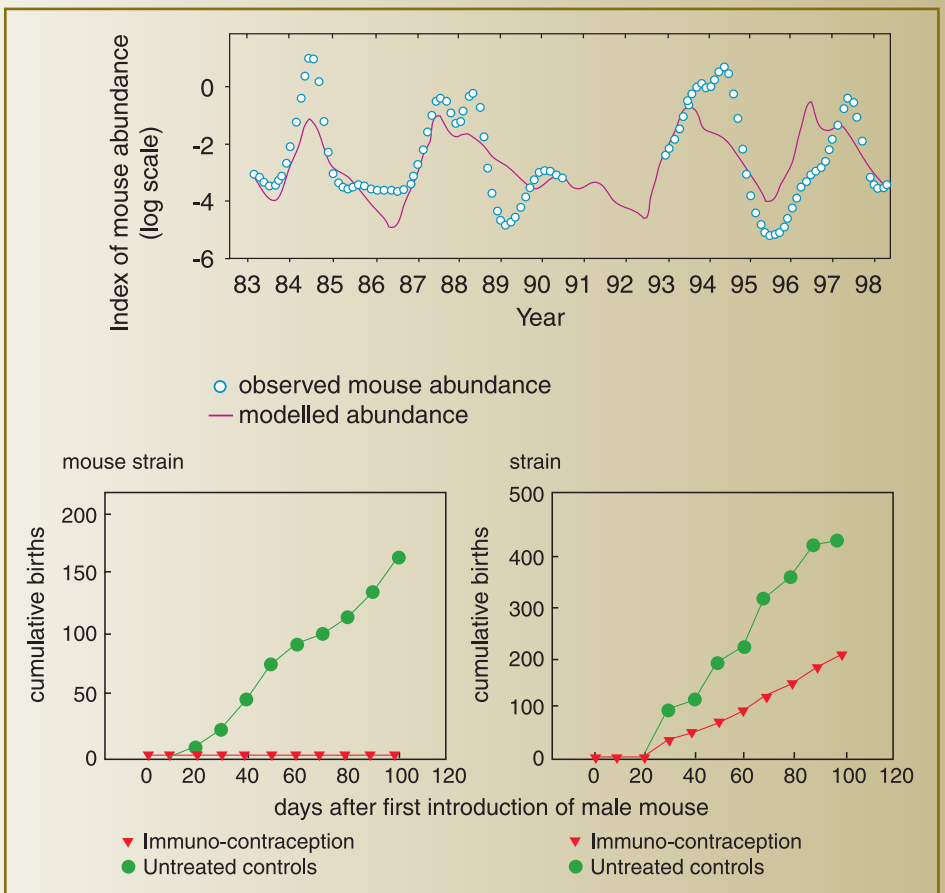
Mal Lawson's group has succeeded in making recombinant cytomegalovirus by inserting the genes responsible for the ZPC protein (antigen) into the DNA of the virus. When they infected several laboratory strains of mouse with this modified virus, they observed various degrees of contraception. One susceptible strain produced no litters for 200 days after immuno-contraception, while untreated control mice produced about 250–350 young (see the graphs). The scientists obtained similar impressive results with a group of wild mice kept in the laboratory.

What proportion of a mouse population needs to be sterilised?

Singleton's group investigated this in wild mice that they confined to pens in the Mallee wheatlands of Victoria. The researchers simulated immuno-contraception by tubal ligation of female mice (tying the tubes of the uterus by delicate surgery). Their studies indicated that sterilising about two-thirds of a female population would be sufficient to prevent plagues of mice.



Here a mouse virus is employed to deliver the antigen (a protein from a mouse egg or sperm) that triggers an immune response in the mouse – against its own reproductive cells. Mouse genes (DNA) for a mouse egg (or sperm) protein are incorporated into the virus and the modified virus is introduced to the mouse population. When the virus infects mouse cells, it causes them to produce the reproductive proteins (and viral proteins) on their surface. The mouse's immune system produces antibodies against the reproductive protein and these spread to the reproductive organs where they bind to either the egg or the sperm and so block fertilisation.



Upper graph: Modelling mouse numbers. A mathematical model for mouse abundance in the Mallee wheatbelt has been able to account for most mouse outbreaks between 1983 and 1998. Models such as this are being adapted for assessing the effectiveness of mouse control methods, including immuno-contraception.

Lower graphs: When mice were infected with the modified virus carrying genes for the mouse-egg protein ZPC, various degrees of immuno-contraception were achieved. The untreated control groups bred 'like mice'.

Gnawing away at **species richness**

RODENTS can have a dramatic impact on ecosystems. Perhaps the classic illustration of this is the industrious engineering activity of the beaver in North America. Beavers gnaw down trees to build up to 16 dams per kilometre of stream, radically altering the hydrological and biological character of the watercourse.

The house mouse, smaller in size but able to attain great abundance, can also modify environments and affect other species, according to Dr Chris Dickman of the School of Biological Sciences, University of Sydney.

'When mice in agricultural settings reach plague proportions, they obviously cause great damage to crops. However, feral mice can also have more subtle effects on more natural, less-modified environments,' Dickman says.

When he studied the impact of the house mouse (*Mus domesticus*) on Boullanger Island, Western Australia, Dickman discovered that mice were depressing the species diversity of invertebrates, especially beetles and spiders that they were eating. Invertebrate species richness increased by 3% when the scientist removed mice, whereas in control plots (that still had mice) it decreased by 18%.

Mouse removal from plots also allowed an increase in litter depth and this happened within just three months. 'Capture rates of small skinks increased by up to 35% following mouse removal, presumably because the deeper litter layer afforded more shelter for the lizards and because of the more diverse invertebrate food resource,' Dickman says.

'Rodents interact extensively with their environment, often in a beneficial way, but here foraging by an introduced mouse species has had a negative effect on an island ecosystem.'

The house mice can modify environments and affect other species. On Boullanger Island, Western Australia, mice were found to be depressing the species diversity of invertebrates and skinks.

These early results are promising, but many questions remain. Will the method sterilise wild strains of mice, previously infected with cytomegalovirus? Will the genetically modified virus vector spread and persist as well as the wild-type virus, and so on?

Modelling mouse and virus

In addition to studies with penned mice, the team intends to employ a computer model to answer questions about the behaviour or epidemiology of the virus in wild mouse populations. Singleton and his colleagues at the CRC, including Dr Roger Pech, Dr Greg Hood, Peter Brown and Stephen Davis, are refining a model recently developed at the centre to help explain and ultimately predict mouse plagues in the wheat-lands of the Victorian Mallee region. It was designed to provide farmers with early warning of eruptions in mouse abundance.

The Mallee model uses mathematical equations to simulate and predict the numerical responses of mouse populations to changes in food availability, particularly wheat and grass seeds. That is, it works on the premise that mouse numbers reflect annual pulses of food, the magnitude and duration of which are determined by the weather. The trigger for mouse plagues in the region tends to be high rainfall in the autumn or winter before the breeding season.

Abstract: Under the right conditions, mouse populations can quickly become plagues, causing costly grain losses in the wheat-sheep belts of eastern and southern Australia. Scientists at Canberra's Pest Animal Control Cooperative Research Centre are using immuno-contraception – contraception through manipulation of the immune system – to prevent successful breeding. Fertility control is intended to slow population growth so that the pest does not exceed numbers at which economic damage is unacceptable. The antigen is being delivered by inserting its genes into those of a naturally-occurring, non-fatal mouse virus. A proportion of the mouse population will be sterilised and population growth slowed. Results of laboratory and cage experiments have been promising. Computer modelling is being used to study the behaviour or epidemiology of the virus in wild mouse populations.

Keywords: mice; *Mus domesticus*; feral animals pest control; contraception; immuno-contraception; murine cytomegalovirus (MCMV); viruses; immune responses; computer models; mouse plagues.

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The effect of so-called density-dependent factors such as predation, disease and dispersal – that have a proportionally greater effect on mouse numbers when population densities are high – is included in the model. It takes the form of an additional factor in the model that is a surrogate for all of these processes.

This particular model does a reasonable job of predicting the rate of increase and abundance of mice in the Mallee (see the graph on page 29). However, it needs further modification before it can accurately assess the likely effectiveness of mouse control programs such as immuno-contraception. This is where the modellers are concentrating their efforts.

If strong opposition to the release of a genetically modified organism emerges, the researchers have another plan. They can, more simply, opt to incorporate dead engineered virus particles, complete with antigen, into a harmless rodent bait. This form of immuno-contraception would not transmit from mouse-to-mouse like the live virus and so would be more expensive. It would also be more difficult to sterilise two-thirds of the female mice in a population and maintain a long-lasting effect using non-toxic contraceptive baits.

The scientists believe that immuno-contraception using a live virus carrier is more likely to achieve the desired result: humane and effective long-term control of the, remarkably prolific, feral mouse.

More about rodent control

Singleton G Hinds L Leirs, H and Zhang Z eds (1999) *Ecologically-based Management of Rodent Pests.* Australian Centre for International Agricultural Research, Canberra.

More information about rodent research can be found on the web at www.dwe.csiro.au/research/progv/rodents

Top: Mice in a pitfall trap.

Above: Mice flee as the cover of a bait station is lifted. Immuno-contraception could complement or replace control methods that kill mice.

Below: The new virus-delivered control method is being assessed in large pens in the Victorian wheat-belt.