SHOULD IMMUNOCONTRACEPTION BE USED FOR WILDLIFE POPULATION MANAGEMENT?

D.W. COOPER


Immunocontraception involves eliciting an immune response against eggs, sperm or hormones so that successful reproduction is prevented. Work in Australasia is aimed at European rabbits (Oryctolagus cuniculus), red foxes (Vulpes vulpes), house mice (Mus musculus), common brushtail possums (Trichosurus vulpecula), koalas (Phascolarctos cinereus) and kangaroos (Macropus spp.), with the vaccines involved all containing self antigens or their relatives. Two fundamental problems have been inadequately addressed in this research. The first problem is that it is difficult to obtain strong immune responses against self antigens and so the vaccines may be ineffective. Most published data on the effect of immunocontraceptives on reproduction involve the use of an adjuvant of which there are many kinds. The materials enhance the immune response greatly. The most frequently used is Freund’s adjuvant which can cause chronic suffering. Its use on wildlife will lead to very negative public perceptions. There has been no convincing demonstration that successful immunocontraception is possible with any method of vaccination likely to be used in the field, if success is defined as contraception of a proportion of the population high enough for management requirements. If it is assumed that success can be achieved, the second fundamental problem arises with two potential consequences. Even with adjuvant, a substantial minority of the vaccinated animals remains fertile. The first consequence is that since failure to be contracepted is likely to be in part genetic, there is likely to be rapid selection for these non-responders. The method will become ineffective in a few generations. The second problem is that the offspring of the animals which breed will have altered immune responses. Their capacities to respond to their own pathogens or to harbor pathogens of other species in the same ecosystem are likely to be changed. The presence of chlamydia in P. cinereus and bovine tuberculosis in New Zealand T. vulpecula means that responses to these pathogens would have to be studied in offspring of immunocontracepted parents to ensure that the offspring were not more susceptible to them. New Zealand intentions to put an immunocontraceptive into a T. vulpecula gut worm must be viewed with caution by Australia. The eggs of transgenic worms will be easily transplanted either accidentally or deliberately back into Australia, and so infect T. vulpecula in Australia.

Key words: immunocontraception, fertility, vaccination, kangaroo, possum, koala.

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HOW to regulate the numbers in wildlife populations is a question of concern around the world. Issues of efficacy and of ethics are continually raised. Older methods, which involve shooting, poisoning, trapping or pathogenic agents are increasingly being questioned, especially by animal welfare organizations (Animals Australia 2002). The animals most frequently at issue are usually large and are regarded as being valuable, beautiful or having cultural significance. They include koalas (Phascolarctos cinereus) in Australia, elephants (Loxodonta africana) in Africa, deer (e.g., Odocoileus and Cervus spp.) in the United States of America and seals (Phocidae) in many countries. Some species are deeply unpopular in the countries to which they have been introduced where they have become pests, but this perception is not shared by the source countries. Examples include Australian common brushtail possums (Trichosurus vulpecula) introduced to New Zealand or English red foxes (Vulpes vulpes) and European rabbits (Oryctolagus cuniculus) introduced into Australia. The scientific activity which the issue of wildlife population management has generated has been frequently summarised (e.g., Bradley 1994; Cowan 1996; Kreeger 1997; Austin 1998; Robert 1998; Environment Australia 1999a,b,c; Pest Animal Control CRC 2000-2001).
For most populations it is possible to give a set of requirements for any population regulation method. It must be:

1. Feasible. That is, it will actually stabilize or reduce numbers over long periods.
2. Cost-effective. That is, the money available is usually quite limited, even in rich countries.
3. Humane. That is, the animals themselves should not suffer and violence should be avoided.
4. Without side effects. That is, other components of the ecological system in which the species lives should not be adversely affected.
5. Internationally acceptable. That is, the management method adopted should not affect the same or similar species in other countries. This is especially true of any immunocontraceptive spread by a live vector.

In order to achieve these goals, research aimed at finding methods which fulfil these requirements has increasingly shifted towards fertility control. One method which has had widespread support is immunocontraception (Tyndale-Biscoe 1994; Kirkpatrick et al. 1997; Bradley et al. 1999; Frayne and Hall 1999). In this method, animals are induced to mount an immune attack against a component of their own reproductive system such that they become infertile. This could be against eggs, sperm or a hormone necessary for successful reproduction. In reality, most of the research has concentrated on immunising females against the proteins which surround the egg, which are called the zona pellucida. There have been two sources, either whole pig (Sus scrofa) zona pellucida (PZP) or a recombinant form of one of them (ZP3). The research along these lines has also had stimulus from alternatives to use the same approach to find a long term contraceptive for humans (Aitken et al. 1993; Dimhofer and Beyer 1995; Jones 1996; Castle and Deane 1996; Paterson et al. 1998; Baird 2000).

The purpose of this review is to examine how well immunocontraception fulfils the five criteria listed above. I conclude with a brief examination of research policy directed towards wildlife management in Australia and New Zealand.

REQUIREMENTS FOR A SUCCESSFUL IMMUNOCONTRACEPTIVE

Feasibility

This has been addressed by Cooper and Herbert (2001). A large literature exists on the immunological responses to a number of components of the reproductive system but literature on trials of the effects of immunocontraceptive vaccines on reproduction is small. These trials all have features in common, and so do their outcomes. The vaccine must be given at least twice and it is given in conjunction with material called adjuvant. Adjuvant ensures that weak antigens will elicit a response. Immunocontraceptive vaccines usually contain weak antigens because they are closely related to self components. The outcome in several trials has been to achieve 89% reduction in fertility for PZP used on feral donkeys (Equus asinus) (Turner et al. 1996), to none at all for recombinant antigens used on white tailed deer (Odocoileus virginianus) (Miller et al. 2000), where relative fertility is defined as the number of offspring for females in the vaccinated group divided by the same figure for the control (i.e., unimmunised females).

Some research has implicitly recognised the non-responder problem and attempted to solve it biotechnologically. Immune responses are regulated by cytokines. In an attempt to overcome resistance to mouse pox found in some inbred house mouse (Mus musculus) lines, Jackson et al. (2001) used virus expressed mouse interleukin-4. Infection of recently immunised genetically resistant mice with virus expressing this cytokine resulted in significant mortality due to fulminant mouse pox. This caused widespread concern that a method of creating killer viruses had been created, with potential as a bioweapon (Finkel 2001).

The requirements for multiple injections and the failure to obtain contraception of all members of the population make the method impractical. Multiple vaccinations raise costs. The fact that some contracepted or vaccinated animals reproduce implies that genetic selection for non-responders to the vaccine is possible. Tables 1 and 2 give some idea of the change in one generation, for given levels of non-response and of heritability. Note that these figures

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<th>General population incidence of non-responders (%)</th>
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Table 1. General population incidence (%) after one generation of complete selection of both sexes, i.e., all responders are contracepted (after Falconer 1964).

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Table 2. Number of generations required to exceed more than 20% non-responders with complete selection (after Falconer 1964).
refer to selection on both sexes. If selection is on one sex, the heritability is approximately halved. Even so, selection for non-responders is rapid. Barlow (1997) has modelled the effect of immunocontraception on New Zealand T. vulpecula populations. Effective population control may imply that 80% of the females require contraception. Selection for non-responders quickly causes this figure to be unrealisable.

**Cost-effectiveness**

In addition to the need to capture (or perhaps dart) each animal twice, there is the cost of the vaccine and its delivery. Recombinant products are likely to be orders of magnitude more costly to produce than small molecular weight poisons. One way around this is to incorporate the recombinant genes into plants and immunise via the oral route (Smith et al. 1997). Immunisation leading to contraception by this method has yet to be demonstrated.

**Humaneness**

Immunocoutraception is often advocated as an humane method. In its present form it is not. The requirement for adjuvant means that the vaccinated animals probably suffer long-term pain. The use of adjuvant is increasingly being questioned, even for laboratory animals (Hanly et al. 1994; Leenaar et al. 1995). The most widely used adjuvant is called Freund’s adjuvant. In its complete form it consists of alum salts, killed mycobacteria and a mineral oil. Its use can lead to painful lesions and alternatives are now recommended. However, the two examples where alternatives were used were also less successful in reducing fertility: grey seals (Halichoerus grypus) (Brown et al. 1996, 1997) and L. africana (Fayrer-Hosken et al. 1999, 2000). Its use on wild animals (e.g., P. cinereus) is especially open to question (Kitchener et al. 2001).

**Ecological ‘side-effects’**

This is perhaps the most dangerous aspect of the use of immunocoutraception and is the least commented on (Nettles 1997). The physiological function of the immune system is to protect against infectious diseases. Because continued application of immunocoutraception over a period of generations will select for animals which do not respond, the genetic composition of the population will change with respect to its ability to mount immune responses. This is of course also true of the use of pathogens such as myxomatosis (Kerr and Best 1998) and calicivirus used to control populations of O. cuniculus. The difference between selection by immunocoutraception and by pathogens is that, in general, the former will select for reduced immunological capacity while the latter does the opposite. Before immunocontraception could be used on New Zealand T. vulpecula it would be necessary to study the relationship between their immune responses to bovine tuberculosis and to the immunocontraceptive vaccine. Similar remarks apply to response to chlamydia and to immunocontraception in P. cinereus.

A completely unstudied problem is the possible acquisition of micro-organisms by the target species which are in fact pathogens for other species in the same ecosystem. This could also result from genetic changes to the target species’ immune system. Given the number of species of micro-organisms and the number of vertebrate species in the same ecosystem, this becomes a problem of daunting complexity.

**International issues**

Pests in one country are highly valued species in others. Management measures aimed at the pest should not reach the highly valued conspecifics elsewhere. The point is illustrated by T. vulpecula. New Zealand scientists have planned to put genes for immunocontraceptive proteins into the genome of a brush-tailed possum parasite Parastrongyloides trichosuri (Ralston et al. 2001). The aim is to use a GE (genetically engineered) form of the species as the vector to vaccinate New Zealand T. vulpecula. It is very doubtful whether this will be acceptable to Australia. The eggs of this parasite are shed into the possums’ faeces. They are relatively long-lived. If the GE form spreads in New Zealand, these eggs will quickly be carried back to Australia on the shoes of the hundreds of thousands of Australians who visit New Zealand annually, and by this means reach suburban gardens and the T. vulpecula they contain. Similarly, many countries will be apprehensive if Australia succeeds in constructing virus vectored immunocontraceptives for O. cuniculus and V. vulpes (Williams 1997).

**RESEARCH POLICY ISSUES**

It is apparent that a series of basic scientific issues must be resolved if immunocoutraception is to become effective for population control. If this is achieved, issues regarding its safety then remain. The resources which have been devoted to research on immunocoutraception over the last decade have been considerable. In Australia and New Zealand the two Cooperative Research Centres (Marsupial CRC and Pest Animal CRC – see their most recent Annual Reports) alone have spent tens of millions of dollars. While results of fundamental scientific value have emerged, it is not clear whether or when anything of practical significance for wildlife management will be available. Unrealistic expectations have been raised. For example, Bradley et al. (1997) discussed the possibility of a bait-delivered vaccine for V.
vulpes by 2002. Given that other approaches (e.g., fencing, 1080 poisoning) and the use of hormonal implants have proven value (Cooper and Herbert, 2001), a reassessment of the balance of funding for wildlife management is now needed. In my view, a very strong case exists for devoting increased resources to making 1080 use more humane by using it in conjunction with an anaesthetic (Marks et al. 2000). This poison is cheap and effective, although public misgiving about its humaneness could limit its use (see Seawright and Eason (eds) 1993).

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REFERENCES


FRAYNE J AND HALL L, 1999. The potential use of
sperm antigens as targets for immunocontraception; past, present and future. *Journal of Reproductive Immunology* 43: 1-33.


