

# Reproduction



SUPPLEMENT 60

## Fertility Control in Wildlife

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Published by the Society for  
Reproduction and Fertility

[www.srf-reproduction.org/journal](http://www.srf-reproduction.org/journal)

## An overview of the symposium: where have we been and where are we going?

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The Fifth International Symposium on Fertility Control in Wildlife is the continuation of a forum that was first organized in 1987 to address the growing concerns posed by new paradigms in wildlife management. Each of the five symposia has brought together scientists from around the world, many of whom work on the cutting edge of technologies that collectively may move us closer to the solutions for humane and non-lethal control of wildlife populations. Richard Leakey, former Director of the Kenya Wildlife Service, and a long time advocate of non-lethal approaches to the management of Africa's wildlife, eloquently framed both the urgency of the need for wildlife contraceptive technology and the challenges that lie before us.

The historical perspective for this symposium series is interesting and educational. The first symposium, held in Philadelphia in 1987, was largely a historical overview of what had been tried in previous years, mostly without success. The second symposium, held in Melbourne in 1990, was more or less futuristic in nature, exploring what might be possible. By 1993, when the third symposium was held in Denver, it was clear that the history and future were merging, and that practical and successful approaches were finding their way to the field. The 1996 symposium, held on Great Keppel Island, introduced the concept of the biological vector. Now, in 2001, we have still more advances both in the field and the laboratory.

The many experts who came to The Kruger National Park and Skukuza have presented us with an array of possibilities for the non-lethal management of wildlife. Summarizing such a symposium cannot be accomplished easily, as there are some distinctions among needs and approaches that are often overlooked by researchers and the general public alike. Firstly, to reflect on the value of the papers given in this symposium and the ideas they represent, they must each be placed carefully in proper context. For example, there is a world of difference between the approach to fertility control in valued wildlife species, where reversibility, safety and flexibility of application are equal to, or even more important than, efficacy or ease of administration. In contrast, the concept of fertility control of 'pest' species opens the door to a whole spectrum of different approaches and mechanisms. Does anyone care whether a New Zealand possum never returns to fertility after treatment or whether its behaviour is changed significantly? Probably not, but one wouldn't be very wise to suggest that scenario for a North American wild horse or an African elephant.

At one end of this spectrum are the 'valued' species, those that the public perceives as desirable and in need of control, but certainly not eradication. These include the wild horses of North America, genetically valuable captive exotic species in zoos, African elephants and a variety of wildlife in national parks around the world. In Australia, the koala and most of the kangaroo species certainly fit this category. The certainty of where white-tailed deer fit is less

certain, with significant segments of the population viewing them as 'pests' and a similar segment seeing them as desirable.

The 'pest' category includes New Zealand possums, feral pigs anywhere, virtually all ungulates, carnivores and rabbits in Australia, almost all non-native species in national parks on any continent, and most rodents anywhere. As an aside, the rationales for placing these species in the 'valued' or 'pest' categories range from economic to value-based perceptions and are not absolute.

A second context for the work presented in this Symposium is that of regulatory issues. The fascinating, potentially effective and possibly sobering biological vector approaches used by many of the Australian investigators and others will probably never see the light of day in the USA, no matter how benign the agent or the vector. We really have no idea how African nations will view this form of delivery and exactly where European countries will fall on this issue is little better than a guess. In the USA we can't even discuss oral delivery unless the contraceptive agent is species specific. In fact, these issues have driven the very direction of research on entire continents.

Finally, the entire issue of wildlife contraception rests within diverse and often contentious views of the ethics of this still arcane approach to wildlife management. What seems ethical and moral to one person often seems outrageous to others. This, together with economic, conservation, philosophical, cultural, political and social values tends to create a wide diversity of opinions about whether we are making progress or sliding backwards. Thus, today I will try to provide some sort of useful summary despite these wide-ranging differences in context.

My last observation before examining the specific content of this symposium is a disappointing one and, frankly, little has changed over the 14 years since the first wildlife contraceptive symposium in Philadelphia. Although the 'research in progress' dimensions of wildlife fertility control are impressive, and a great deal of the work can be described as elegant and exciting, the actual application of fertility control to free-ranging wild populations remains limited. Of the 45 papers given at this symposium, only seven involve free-ranging wildlife. At the same time, the urgency for more application to animals in need increases annually at alarming rates. It is one thing to study wildlife contraception in a pen and yet another to come face to face with the realities of delivering contraceptives to intelligent, wily, sometimes dangerous and always clever free-roaming animals. Thus, this is a call to move more rapidly from those laboratories and pens to the field to accomplish the task before us, rather than just publish more papers.

### Zona pellucida vaccines

As with previous symposia, the porcine zona pellucida (PZP) vaccine remains the vaccine that is studied or applied most commonly to wildlife species. Rick Naugle's efforts on Fire Island National Seashore with wild white-tailed deer (*Odocoileus virginianus*) have demonstrated the high degree of contraceptive efficacy and safety of this vaccine, and, more importantly, that we can reduce deer populations with contraception. Paul Curtis has confirmed this same level of efficacy in deer, as well as the phenomenon of multiple oestrous cycles in PZP-treated deer, reported almost a decade ago, and his observation regarding changes in bone marrow in treated animals warrants further investigation. Richard Fayer-Hosken has provided us with a good look at the comparative antibody responses and the role of adjuvants across different species. Similar contraceptive responses have been demonstrated in brushtail possums (*Trichosurus vulpecula*) by Janine Duckworth, in Eastern grey kangaroos (*Macropus giganteus*) by D. J. Kay and in elk (*Cervus elaphus nannodes*) by Susan Shideler. Indeed, in our own work with zoo animals, more

than 95 species have been treated and there are sufficient data to report success with more than 60; thus, it is likely that PZP will work in virtually all mammalian species.

Two important advances needed for the development of more practical applications of PZP in the field are: (i) a single-inoculation format that eliminates the need for a booster inoculation during the first year of treatment; and (ii) development of recombinant forms of the vaccine glycoprotein to eliminate the labour-intensive and, therefore, limited production of native PZP. Interestingly, and a bit discouraging at the same time, is the reality that these two priorities have not changed since they were first articulated in 1993 in Denver, nor have they been conquered. The review by John Turner has provided at least one model for a single-inoculation form of PZP delivery, through lactide-glycolide microspheres and pellets, and the evolution of this research provides us with an interesting perspective for understanding the snail-like speed of progress. In mares, the better part of a year is required to recover data on a single-inoculation vaccine and there are few shortcuts. Despite this reported progress, there are other formats that must be tested and which might provide even more practical single-inoculation formulations.

Bonnie Dunbar has summarized quite succinctly the scientific and ethical issues of recombinant vaccine design. This is an important issue because practical logistical considerations with native vaccines, such as the PZP vaccine and the labour-intensive production attendant to such native preparations, will always be limiting factors in their application. The appearance of successful synthetics or recombinants will rest on the ability to recognize appropriate epitopes for permanent and reversible contraception, species specificity of these epitopes, and adequate and accurate glycosylation of the protein foundations. In the end, practical wildlife contraception rests on this achievement as much as any other dimension of this still arcane science.

Some of these approaches, used by Janine Duckworth, have already produced an apparently successful vaccine and subsequent contraception in brushtail possums, and in koralas (*Phascogalea cinerea*), by Ann Kitchener. Chris Hardy's elegant work with recombinant murine epitopes shows a great deal of promise. More emphasis must be placed on this line of research if we are ever to reach the full potential for wildlife management by fertility control. Other manipulations of the native PZP vaccine, such as conjugation to other immunogenic molecules, demonstrated by Matt Barber, in which he caused some contraception in domestic pigs, may provide additional pathways to effective vaccine development.

Significant progress has been made in understanding the long-term safety of the PZP vaccine; at least in mares. In our work with wild mares, now stretching over 14 years, we see the reality and the limits of reversibility of contraceptive effects, and it is also clear that this vaccine is extremely safe to give to pregnant mares, with no effects on pregnancies in progress, health of the foals or subsequent survival. Although not reported here in this symposium, these safety data for mares were also reflected recently in PZP-treated African elephants (*Loxodonta africana*), suggesting that the safety of this vaccine will extend across many species.

### GnRH vaccines and agonists

The second largest number of reports here dealt with GnRH vaccines and agonists, which is similar to past symposia. Paul Curtis has demonstrated the usefulness of a GnRH vaccine in white-tailed deer, with contraceptive results similar to PZP. The exciting work by Dan Baker, in which he successfully applied the commercial GnRH agonist leuprolide to elk in a subcutaneous bioimplant, points the way to new approaches for ungulates. Equally important was his observation that reproductive behaviours were not changed. However, a remote

delivery system must still be developed before this becomes practical outside zoos. Janine Brown has demonstrated the inability of deslorelin to suppress oestrus in Asian elephants, but confirmed the utility of remote endocrine monitoring, which has been a valuable tool in wildlife contraceptive studies for almost 15 years.

Within the context of captive exotic species, contraception of carnivores remains most problematic. While human contraceptives work well for primates, and the PZP vaccine appears to work across the entire breadth of ungulate species, carnivores have proven resistant to effective and safe contraception. However, the reports by Henk Bertschinger and Tim Trigg, using GnRH analogues in felids and canids, are encouraging. The compounds worked well in both sexes and the resultant contraception appears to be reversible. The only serious problems identified so far are the loss of male-related secondary sex characteristics in males, and some species-specific variability in efficacy.

Perhaps one of the most exciting advances in wildlife contraception has been provided by Terry Nett's work. The conjugation of a plant cytotoxin to a GnRH agonist resulted in the significant reduction in LH secretion in mule deer (*Odocoileus hemionus*). The cytotoxin remains harmless to other tissues except where it is delivered by the carrier to a specific target cell, in this case to the LH-producing cells of the pituitary. Although a great deal more work remains to be carried out, this is one of the most innovative and original ideas to grace this symposium.

### Steroids

One trend that has been clear since 1987 is the decline in the use of steroids as potential fertility inhibitors in wildlife, particularly in free-roaming populations. The use of Depo-Provera™ in the hippopotamus (*Hippopotamus amphibius*) was shown by Laura Graham to be capable of shortening the luteal phase in this species and was safe to give to pregnant animals. Its usefulness in preventing pregnancy will depend on determining effective doses. Chris Nave's experiments with levonorgestrel implants were extremely successful in demonstrating reversible contraception in the grey kangaroo and the implants were also safe to give to pregnant and lactating animals. The application of these contraceptives to free-roaming wildlife would be difficult because of the inability to deliver the compounds remotely, and the issue of passage through the food chain has not been addressed, but their use in captive populations remains feasible. Linda Munson's long-standing and ongoing work regarding the potential for contraceptive-associated pathologies is important to consider here. While she asks us to examine this issue with all contraceptives, her work has clearly raised concern over the use of steroids in certain species. Beyond that, her work provides us with a framework for studying safety with other compounds and vaccines.

### Other approaches

A variety of other approaches has been suggested in this symposium. Twink Allen's work presented us with a detailed look at the hormonal control of pregnancy in the elephant, and provides evidence that the ovary exclusively supports the hormones of pregnancy in this species. This, in turn, opens the door to the use of abortifacients in elephants, if public opinion does not rise up to create large social hurdles. Frank Boue's delivery of sperm-specific antigens to foxes (*Vulpes vulpes*) shows some promise if tissue specificity can be demonstrated, and there is a viral vector that might provide a delivery system.

Dopamine agonists are suggested as possible useful compounds by Graham Coulson, citing several previous studies with various forms of bromocriptine; however, Thomas DeLiberto

has shown that the dopamine agonist cabergoline was ineffective in coyotes (*Canis latrans*), presumably because prolactin has no luteotrophic effects in this species.

### Modelling

An area of growing interest but also growing concern is that of modelling for various contraceptive approaches for wildlife. The questions being asked by Lyn Hinds and Phil Cowan and other investigators are critical to the ultimate success of wildlife contraception but, at the same time, the paucity of actual field applications has led to models that are based on many assumptions instead of hard data. About the only generalizations that can be made at this point are that contraception may well be effective in reducing populations of short-lived species with high natural mortality, as shown by Roger Pech, Dave Ramsey, Grant Singleton, Nigel Barlow and Stephen Davis, and that in long-lived species with low mortality rates the best anyone can expect is short-term zero-population growth and a very intense effort over a very long time to achieve reductions. Stephen Davis brought our attention to factors which have become assumptions but which have not been well investigated, including changes in natural regulatory mechanisms, subordinate females breeding and density-dependent changes in fertility. There are even fewer data for long-lived species and the surprising findings through our own work with wild horses suggest that decreased mortality and increased longevity must be accounted for in newer models.

### Viral vectors

One of the most controversial issues in the subject of wildlife contraception is that of biological vectors for the delivery of contraceptives. Gerhard Reubel and Frank Boue have explored the use of various organisms and, in particular, non-pathogenic viruses, as vectors for contraceptive vaccine delivery. Although the pragmatism of such an approach is self-evident, the questions of species specificity, mutating viruses and methods that once unleashed cannot be called back must be addressed, and the answers must be forthcoming before either the public or the regulatory agencies will sign off on this approach. If anyone at this symposium had any doubts about the complexity of the regulatory process for these genetically modified organisms in Australia, Kent Williams has put that issue to rest.

### Field applications

Despite the small number of actual field applications, some important new information has been generated. Rick Naugle's pioneering work on Fire Island with white-tailed deer is one of the first studies to demonstrate the ability to alter population profiles significantly, the ultimate goal of wildlife contraception, with a significant reduction in the treated population over 7 years. It should be mentioned here that field application moves the discipline of wildlife contraception from pure science to almost pure art, and unless efficient delivery systems are studied and developed, the science will amount to very little. Even more challenging was the work of Susan Shideler with the free-ranging elk of Point Reyes National Seashore, where the logistics of treatment ranged from helicopter capture to hiding behind saddle horses for the purpose of darting animals with the booster inoculations, but which at the same time provided the first suggestion that elk populations could be altered with this technology. Finally, our own work with the wild horses of Assateague over 14 years has also demonstrated the ability to achieve zero population growth in a very short time even in long-lived species, and equally

important, the long-term safety of the PZP vaccine, in terms of reversibility, longevity, general body condition and application in pregnant animals.

### Behaviour

Only three papers on the issue of behaviour have graced this symposium. And Delsink's work with PZP-treated elephants north of here in Makalali Game Reserve begins to extend the very preliminary behavioural work started here in Kruger Park by J. J. Van Altena, and will be critical to the acceptance of elephant immunocontraception by various animal protection groups. Glen Saunders' work with toxes and Dave Ramsey's work with possums have illustrated how fertility control may impact on behaviour and how behaviour may influence the use of contraceptives. The real point here is that wildlife populations must not just be controlled, but must be left with their social behaviour and organization intact, or we have defeated ourselves and harmed the wildlife in the process of trying to help it.

### Ethics

The ethical issues permeating wildlife contraception are multiple and complex, and their understanding by those of us who pursue this science is absolutely critical to the ultimate success we achieve in reaching our goals of humane and non-lethal management tools. The wildlife we pursue with this technology is not the exclusive domain of the animal protection community, nor of the governmental agencies that manage wildlife. It is not the exclusive domain of any industry, including agriculture. In addition, it is emphatically not the exclusive domain of scientists. The wildlife we pursue with this technology ultimately belongs to a larger public and we cannot ignore their concerns. Priscilla Cohn, who, incidentally, was instrumental in starting these symposia so many years ago, provided us with an interesting philosophical look at the differences between lethal and non-lethal approaches from the animal rights viewpoint that, if it isn't good for humans, it isn't good for animals. Gwen Curtis gave us a peek into the concerns and opinions of the general public and I can tell you with great assurance, after 30 years in this business, that her findings are not an artefact. John Grandy presented the animal welfare point of view, where concerns extend to validating the need for any management at all, and the criteria for the decision to use this technology and just who makes the decisions, as well as the benefit:cost ratios for the wellbeing of the animals themselves.

Finally, the strident dialogue that erupted in this symposium with regard to biological vectors and vaccine safety is entirely appropriate in a forum such as this one. This dialogue was only a reflection of long-simmering philosophical and ethical issues, which began in 1993 at the Denver symposium, with the introduction of viral vectored and genetically modified delivery systems into the wildlife contraceptive milieu. We should not be dismayed because we, as a scientific community, have some major differences of opinion. Whether we like the idea or not, we here at this symposium reflect the same differences of opinion that exist within the general public. Regardless of the philosophical view one takes, either animal rights or animal welfare, or any other stance, it is clear that these views originate with the public, and that the scientists who produce the technology must listen carefully.

### Where next?

If the true goal is to provide non-lethal, humane and publicly acceptable management tools for wildlife populations, then the priorities are clear. In what seems like an echo from the last symposium, we still need that single-inoculation reversible vaccine and it is closer today than

it was 5 years ago. We also need synthetic contraceptives that can be produced in large quantities and inexpensively. The diversity of wildlife problems requires that we have both reversible contraceptives and non-reversible sterilents, and there must be more studies of the behavioural consequences of wildlife contraception. Better population models based on genuine field data must be forthcoming if we are to know how to use this management tool wisely. There must be a clear identification of the ethical and moral issues surrounding our stewardship of wildlife, and of the precise role and place of fertility control in management ethics. Finally, we must move this technology, where it is safe to do so, into the field in actual applications more rapidly than we have done in the past.