causes) and 17 (68 percent) produced foals, which was not significantly different from foaling rates of control mares.

Immunization against GnRH has also been attempted in the stallion (Dowsett et al. 1991). Four weanling colts were passively immunized, either intramuscularly or subcutaneously, with an anti-GnRH antibody (Peptide Technology, Ltd., Sydney, Australia) and given booster inoculations approximately 75 days later. Colts immunized intramuscularly maintained plasma testosterone concentrations of < 0.15 ng/mL (equivalent to concentrations in geldings) for 5 months following the booster inoculations. Thereafter, testosterone concentrations rose to control levels for yearlings. Colts immunized subcutaneously had slightly increased plasma testosterone concentrations (up to 0.37 ng/mL) between the two immunizations but decreased concentrations similar to those seen in the intramuscularly injected group after the second inoculation. Antibody titers were generally higher in the colts immunized intramuscularly, although sexual development was effectively delayed for 12 months in both groups of colts.

A second immunocontraception strategy for equids was based on the identification of antibodies directed against the zona pellucida of the ovum in naturally infertile mares (Liu and Shivers 1982) and immunological cross-reactivity of equine zona-positive antisera and porcine sperm binding (Shivers and Liu 1982). Liu et al. (1989) immunized 10 captive wild mares and 4 domestic mares with the protein equivalent of 2,000 to 5,000 porcine zonae pellucidae. FCA was used for the first inoculation and Freund's Incomplete Adjuvant (FIA) for the three monthly booster inoculations that followed. Of the 14 treated mares, 13 failed to conceive during the first year. The four domestic mares all conceived during the second year after antibody titers decreased.

A field test of the PZP vaccine was carried out on Assateague Island National Seashore (Kirkpatrick et al. 1990). For the test, 26 wild mares were remotely inoculated with approximately 5,000 porcine zonae pellucidae (65 µg protein) and FCA in March 1988 by means of barbless darts. The mares received a second inoculation with PZP + FIA 2 weeks later, and 18 of the mares received a third inoculation with that combination 1 month later. No foals were produced by the treated mares, whereas 50 percent of the 6 sham-injected mares (controls) produced foals, and 45 percent of 11 untreated mares produced foals. Post-treatment foaling rate for the PZP-treated mares was significantly different *(P* < 0.002) than that for the 2 pretreatment years, for sham-treated control mares and for untreated mares. Of the 26 PZP-treated mares, 14 were pregnant at the time of inoculation, and all 14 produced healthy foals 2–3 months following PZP treatment. Thus, the PZP vaccine had no effect on pregnancies in progress or the health of the foals born. Social behaviors and organization were also unaffected by treatment. Once antigen recognition had taken place, a single annual booster inoculation was sufficient to maintain contraception.

In March 1989, 14 of the previously treated mares were given a single booster inoculation. A year later, only one foal was produced. The 12 mares immunized in 1988 but not given a booster in 1989 produced 5 foals, demonstrating for a second time the reversibility of the vaccine's contraceptive effects (Kirkpatrick et al. 1991a). After 6 consecutive years of booster inoculations among the Assateague mares and 104 mare-years (the number of mares treated × the number of years of treatment), four foals have been produced, for an effectiveness of 96 percent. Over the 6-year period, the difference between foaling rates among treated and untreated mares was highly significant *(P* < 0.001).

Field trials were initiated in 1992 with feral donkeys in Virgin Islands National Park. Sixteen adult female donkeys received an initial inoculation of 65 µg of porcine zonae pellucidae + FCA, a second identical inoculation 3 weeks later, and a third 10–12 months later. Eleven untreated adult females were used as controls. Results were not calculated until 12 months after the initial inoculation in order to allow for any pregnancies already in progress at the time of inoculations. Based on observed foals and on fecal steroid analysis (Kirkpatrick et al. 1991b and c), of the treated females, only 1 of 16 (6.2 percent) produced a foal or was pregnant, while among the controls, 6 of

11 (54.5 percent) produced foals or were pregnant. The difference between foaling and pregnancy rates between the two groups was highly significant ($P < 0.01$).

Large-scale field trials with wild horses were initiated in December 1992 in Nevada. Slightly more than 500 wild horses were captured by driving them by helicopter into a trap and portable corrals. Adult mares (n = 131) between the ages of 4 and 12 were included in the study. All mares were freeze-branded with numbers for later identification. One group received two inoculations of PZP about 3 weeks apart with FCA used for the first inoculation and FIA for the second. A second group received only a single inoculation + FCA. A third group received a single inoculation of porcine zonae pellucidae + FCA that contained another 65 µg of pellucidae in lactide–glycolide microspheres. These microspheres were designed to release the antigen over a 4- to 6-week period.

During September 1993, fecal samples were collected from 78 treated or control animals and analyzed for steroid hormones and steroid hormone metabolites, which signal pregnancy (Kirkpatrick et al. 1991b and c). Of 27 untreated mares, 14 (52 percent) were pregnant. Of 17 sham-injected controls, 9 of 17 (53 percent) were pregnant. None of 14 mares receiving 2 inoculations of porcine zonae pellucidae were pregnant. Of 20 mares receiving only a single inoculation of raw pellucidae, 6 (30 percent) were pregnant. No samples were recovered from mares receiving the porcine zonae pellucidae in microspheres.

During June 1994, after aerial foal counts, a total of 65 experimental mares were observed, and foaling results were in general agreement with pregnancy data. From 32 mares that received 2 inoculations, only a single foal was observed. Of 16 sham-treated mares, 10 had foals (63 percent), and of 7 mares receiving only a single inoculation, 3 had foals (43 percent). Of 10 mares receiving a single inoculation of the microencapsulated porcine zonae pellucidae, none had foals. These data suggested a contraceptive effect of a single inoculation with microencapsulated porcine zonae pellucidae that lasted 8–9 months following treatment.

The PZP vaccine has also been tested in captive exotic equids, including 23 Przewalski's horse *(Equus przewalskii)*, 1 onager *(E. hemionus)*, and 26 zebra *(E. zebra grevyi)* (Kirkpatrick et al. 1992b, 1993). Thus far, results are available only for the Przewalski's horses and the onager, and the vaccine has been 100-percent effective in preventing pregnancies in these species (Kirkpatrick et al. 1993). It is better than 80-percent effective in zebras.

Two important issues are raised with regard to PZP immunocontraception of equids. The first is the possibility of long-term effects of the vaccine on ovarian function. PZP-induced contraception is thought to be due to a block to fertilization (Liu et al. 1989). At least two of the major glycopreoteins of the noncellular zona pellucida, ZP3 (Florman and Wassarman 1985) and ZP4 (Hasagawa et al. 1992), are necessary components of the receptor molecule for sperm surface molecules. The role of the ZP3 receptor in the horse has been confirmed in vitro as a zona pellucida-induced acrosome reaction with horse sperm (Arns et al. 1991). The initial study of PZP immunization of horses (Liu et al. 1989) and field tests with the Assateague wild horses (Kirkpatrick et al. 1990, 1991a) demonstrated that the contraceptive effects of PZP immunization were reversible after 1 year of treatment. Plasma progesterone concentrations during the year of treatment indicated a luteal phase and therefore evidence of ovulation. However, the long-term effects of continuous PZP immunization have not been described in either the horse or other species. Reversibility of the contraceptive effect has been demonstrated in several species but only after short-term application of the vaccine (Gulyas et al. 1983, Sacco et al. 1987, Liu et al. 1989).

In the dog and the rabbit, PZP immunization appeared to be very damaging to ovarian follicles and often led to cessation of ovarian function, with accompanying anovulation and depression of estrogen concentrations (Wood et al. 1981, Mahi–Brown et al. 1985). Unusually large doses (5,000 µg) caused anovulation in the baboon (Dunbar et al. 1989). These data suggested that the antibody response of the treated animal attacks not only the zona pellucida of the mature ovum but oocytes and possibly other

Table 1. Antibody titers in response to porcine zonae pellucidae in domestic mares after one inoculation using porcine zonae pellucidae plus PZP-containing microspheres or two inoculations of porcine zonae pellucidae given 3 weeks apart

		Dates of inoculation					
Treatment	Horse	3/13	4/2	4/16	5/7	6/18	10/14
		Antibody titers (% of positive reference serum)					
FCA–PZP bolus & PZP microspheres	Aldo	5	99	114	131	106	79
	Mia	4	70	107	123	82	28
	Imp	6	33	70	95	98	131
	Lab	5	38	76	120	114	39
	Dee	5	56	108	106	99	26
FCA–PZP bolus + FIA–PZP bolus 3 weeks later	Ant	4	90	130	131	152	115
	Con	6	66	145	135	144	58
	Len	8	58	118	123	91	35
	Rou	3	73	116	133	123	79
	Sou	4	67	147	126	136	94

FCA = Freund's Complete adjuvant. FIA = Freund's Incomplete adjuvant.

ovarian tissue with resulting changes in estradiol and progesterone secretion. These effects have not been demonstrated in the horse after short-term use, but there is evidence that these same effects may appear after long-term use.

After 3 consecutive years of PZP treatment, three of seven Assateague mares showed decreased urinary estrogen concentrations and no evidence of ovulation (Kirkpatrick et al. 1992a), and after 6 consecutive years of ovulation, five mares showed no evidence of ovulation. However, three of these five mares showed recurring rhythmic estrogen peaks, suggestive of developing follicular waves, and two of these five mares demonstrated classical estrous behavioral concurrent with an estrogen peak and permitted breeding (Kirkpatrick, unpubl. data). Another mare demonstrated a luteal-phase urinary progesterone metabolite pattern after 5 consecutive years of treatment and 1 year off, suggesting that normal ovarian function returned. The next 3–5 years will provide critical data regarding the effects of the PZP vaccine on ovarian function and reversibility after long-term vaccination with porcine zonae pellucidae.

The second critical issue is related to the number of initial inoculations necessary for contraception. While it has been clearly established that two inoculations, given 3–6 weeks apart, will provide contraception for about a year, the need to give two inoculations decreases the usefulness of the vaccine for wild and feral equids. Thus, the single most important direction for future research is the development of a one-inoculation form of the vaccine which provides at least a full year, and ideally 2–3 years, of contraception protection.

In an initial attempt to develop a one-inoculation PZP vaccine, the PZP antigen was incorporated into nontoxic, biodegradable, 50-μ, homogenous lactide–glycolide microspheres. Upon i.m. injection, the lactide–glycolide material erodes, releasing the anitgen over predetermined periods of time (Eldridge et al. 1989). The carrier itself is metabolized to lactic acid and carbon dioxide.

Five domestic mares were inoculated with an initial bolus of 65 μg of porcine zonae pellucidae + FCA plus another 65 μg of pellucidae contained in microspheres. Antibody titers were compared to titers in mares inoculated with two doses of pellucidae (65 μg PZP/FCA + 65 μg PZP/FIA) given 3 weeks apart. Contraceptive antibody titers lasted for approximately 200 days with the one-inoculation preparation (table 1).

This same preparation was administered to 14 wild mares on Assateague Island. One dart failed to inject. That mare, plus only one other mare, produced foals following treatment. The differences were significant ($P < 0.05$) comparing either 2 foals/14 mares or 1 foal/13 mares (to account for the failed dart) with untreated control mares. Similar research is currently under way to produce a one-inoculation vaccine using microcapsules. The microcapsules are made from the same lactide–glycolide material, but after injection they release the PZP antigen in pulses rather than continuously.

Conclusions

PZP-induced contraception of the mare may be useful to prevent unwanted pregnancies among wild and feral equids. In the case of captive exotic equids, such as the Przewalski's horse and the zebra, contraception may be useful to prevent the expression of undesirable genetic traits ("floppy mane" or the fox allele, for example) or merely to prevent the production of unwanted surplus animals without the need to remove animals and disrupt well-defined social groups. Anti-GnRH vaccines may be useful for the same purpose in the stallion, or simply to reduce aggression among stallion groups. Finally, contraception may represent a publicly acceptable approach to the management of wild and feral horses inhabiting public lands.

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Remotely Delivered Contraception With Needle-less Norgestomet Implants

Darrel J. Kesler

Abstract: A remotely delivered contraceptive was developed that suppressed estrus and prevented pregnancy in deer with 100-percent efficacy. This contraceptive utilized norgestomet, a potent progestin that is approved by the Food and Drug Administration (FDA) for use in cattle. Although the needle-less norgestomet implant is not FDA approved for use in deer, it is safe for treated animals, humans, and the environment. The remote delivery of this implant can be accomplished up to 40 m away and causes minimal tissue damage and stress if administered properly. Because of its ease, its simplicity of delivery, and the control it provides for proper drug handling, the needle-less norgestomet implant holds much promise for control of the overpopulation of deer in the United States. Further, no part of this product will remain to pollute the environment. Although this contraceptive was developed for female deer, preliminary studies suggest that the needle-less norgestomet implant may be effective in males. Widespread use of the needle-less norgestomet implant in deer requires further extensive (and costly) establishment of safety and efficacy as well as FDA approval.

Keywords: Remote delivery, needle-less implants, norgestomet, norethindrone acetate, wildlife contraception, black-tailed deer, white-tailed deer, controlled release, silicone, Food and Drug Administration

Introduction

Deer overpopulation has become a major problem in many areas of the United States. Warren (1991) has presented a detailed review of the historical causes of this problem, the ecological effects of deer overpopulation, and the need for controlling deer populations. Overpopulated deer herds are causing significant economic losses in the form of crop damage, damage to landscape plantings, transmission of diseases to livestock such as cattle (Forbes and Tessaro 1993), and damage to vehicles and humans (injury or death) in deer–vehicle collisions. In many areas, regulated public hunting has been proven to be an effective means of controlling deer populations (Behrend et al. 1970); however, this procedure has become very controversial and political. Contraception of deer may, therefore, be a logical alternative to control deer population.

The purpose of this article is not to provide an extensive review of the literature but rather to review a specific contraceptive (and its development) developed for deer. Because this contraceptive utilizes a steroidal compound, I will refer to other steroids that have been tested for deer contraception, but I will not attempt to provide an extensive review of other contraceptive compounds or procedures.

The selection of a deer contraceptive involves several criteria. The following is a selected list of essential criteria:

- Safety. This involves not only the animals being treated but also the human population and the environment.
- Cost. The product has to be cost effective relative to other methods of population control.
- Efficacy. The product has to be highly effective. Although 100-percent efficacy is not essential, like an equivalent product for humans, it still must be highly effective in preventing unwanted pregnancies.
- Ease of delivery. The product must be uncomplicated and easy to deliver. Even if a product meets the previous three criteria with 100-percent efficacy, it will not be routinely used unless it can be delivered with simplicity and ease.

Several contraceptive systems have been tested in deer and are reported in the literature. None of the developed contraceptives, however, have been accepted with enthusiasm either because of efficacy or because of the difficulty in their delivery. The contraceptive most widely tested is the steroidal compound melengestrol acetate (MGA®; 17α–hydroxy–6–methyl–16–methylenepregna–4,6–diene–3,20–dione; fig. 1) (Budavari 1989, Bell and Peterle 1975, Matschke 1980, Plotka and Seal 1989). MGA is approved by FDA for use in cattle (0.5 mg is orally administered daily; Zimbelman and Smith [1966]) for the suppression of estrus, increased rate of weight gain, improved feed efficiency (Bennett 1993), and, more recently, estrus synchronization in the United States. Another steroid tested is levenorgesterel (also referred to as norgestrel; 13β–ethyl–17α–ethynyl–17β–hydroxygon–4–en–3–one; fig. 1) (Budavari 1989, Plotka and Seal 1989, White et al. 1994). Levenorgesterel is

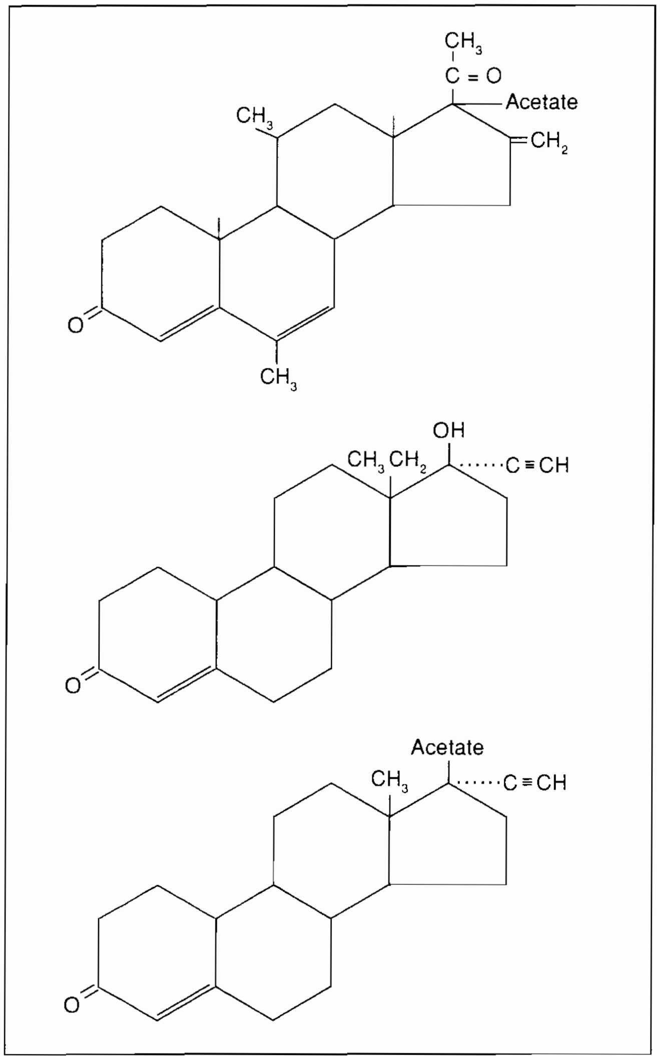

Figure 1. Chemical structures of melengestrol acetate (top), levenorgesterel (middle), and norethindrone acetate (bottom).

the active component of the Norplant® implant approved for human use as a contraceptive implant by FDA in the United States (McCauley and Geller 1992).

Although effective, MGA requires the implantation of a relatively large implant. These implants necessitate capturing the target animal and performing minor surgery for implantation (Plotka and Seal 1989). The implants have been demonstrated to be efficacious for several breeding seasons (Matschke 1980). Levenorgesterel also requires animal restraint for implant placement; however, the implants are smaller than the MGA implants. Unexpectedly, both studies that used levenorgesterel in deer reported that—administered at dosages similar to those used efficaciously in humans—levenorgesterel was not an effective contraceptive in deer (Plotka and Seal 1989, White et. al. 1994).

Both MGA and levenorgesterel were delivered via silicone (polydimethylsiloxane) (Roseman 1972). Because controlled chronic release of steroids in vivo (which is necessary for steroidal contraception) is obtained with silicone implants, and because they are biocompatable in mammals (Dziuk and Cook 1966), silicone proves to be an efficacious delivery system suitable for steroidal compounds in deer (Kesler 1989).

Norethindrone Acetate (NA)

The first compound selected for efficacy evaluation was norethindrone acetate (19–nor–17β–ethynyl–17ß–ol–3–one acetate; fig. 1) (Budavari 1989). Its chemical structure is very similar to that of levenorgesterel. NA is used in combination with ethynylestradiol in the United States (with FDA approval) as an oral contraceptive in humans. A human contraceptive was selected because investigators originally assumed that it would be reasonable to obtain FDA approval (for use in deer) for a compound already approved for a human use. NA was also selected because (1) the acetate provides longer in vivo half-life (Sinkula 1978), and (2) esterification enhances steroid secretion from silicone implants (Christensen and Kesler 1984 and 1986, Kesler et al. 1996). NA implants have been used efficaciously (as a contraceptive) in humans (McCauley and Geller 1992). The first, and last, study (as reported below) was in beef heifers; the compound norgestomet was then selected for evaluation as a deer contraceptive.

Fourteen beef heifers were selected for the study. Heifers were divided into two groups. All heifers had been previously synchronized with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$; Kesler 1985a and b, Kesler and Favero 1989a) and observed for estrus. Twelve days after detected estrus, all heifers were bled, and plasma was assayed by a validated enzyme-linked immunosorbent assay (ELISA) (Kesler et al. 1990) for progesterone concentrations. All 14 heifers had progesterone concentrations greater than 1.5 ng/mL, which suggests that they had corpora lutea that developed subsequent to the previously detected estrus (Kesler et al. 1981). Half (7) of the heifers were subcutaneously implanted with an NA matrix silicone implant. The cylindrical implants, each 3.5 mm in diameter and 2.5 cm in length, were implanted subdermally on the convex surface of the ear. Each treated heifer received one implant that contained 11.5 mg of NA (equivalent to 8.35 mg of norethindrone). At the time of implant insertion, all heifers were administered a luteolytic dose of $PGF_{2\alpha}$. Implants were left in situ for 4 days; after removal, total remaining NA was determined (Kesler et al. 1995 and 1989c). In vitro implant secretion over 4 days was also determined and corrected for in vivo secretion by the procedure reported by Machado (1994).

NA was released from the silicone implants in a typical linearly declining fashion ($r = -0.997$; $y = x(-0.21) + 1.15$) (Ferguson et al. 1988, Kesler and Favero 1989c, Kesler et al. 1995). Over the 4-day period, a total of 2.53 mg (22 percent of the total) was delivered in vivo. Three of the four control heifers (43 percent) were detected in estrus whereas all seven (100 percent) of the treated heifers were detected in estrus (table 1).

Estrus was detected at similar times after $PGF_{2\alpha}$ treatment for both groups. To verify $PGF_{2\alpha}$-induced luteolysis, all heifers were bled 2 days after $PGF_{2\alpha}$ treatment, and plasma was assayed for progesterone concentrations (Kesler et al. 1990). The progesterone concentrations in all heifers suggested that luteolysis was ensuing or had ensued.

In summary, NA did not suppress estrus. In fact, during a period of high NA secretion (2.53 mg over the 4-day period), there was a tendency for more ($P = 0.02$) NA-treated heifers than control heifers to display estrus. Therefore, NA was not considered further.

Table 1. Norethindrone acetate implant secretion and estrus suppression efficacy in beef heifers

Item	Control	Treated
Number	7	7
Number in estrus	3 (43%)	7 (100%)[1]
Mean interval to estrus	61 hours	59 hours
Norethindrone acetate secreted		
Day 1	0	947 µg
Day 2	0	738 µg
Day 3	0	501 µg
Day 4	0	341 µg

[1] Differed from the control group at the 0.02 level of significance.

Norgestomet Chemistry and Physiology

Chemistry

Norgestomet is approved by FDA for use in cattle for estrus synchronization (Darling 1993). The procedure, designated Syncro-Mate B®, includes a 9-day implant containing 6 mg of norgestomet and an intramuscular injection that consists of 3 mg of norgestomet and 5 mg of estradiol valerate that is administered at the time of implant insertion (Chien 1978, Kesler et al. 1995). The purpose of the implant is to suppress estrus. When it is used for estrus synchronization in cattle, subsequent timed breeding (cattle are bred 48–52 hours after implant removal) pregnancy rates range from 40 percent to 60 percent (Odde 1990, Kesler and Favero 1996). Norgestomet has also been successfully used for resynchronization in cattle (Favero et al. 1993 and 1995, Machado 1994, Kesler et al. 1994) and for estrus suppression and synchronization in sheep (Kesler and Favero 1989b and 1997).

Chemically, norgestomet (17α–acetoxy–11β–methyl–19–norpreg–4–ene–20,dione; SC 21009) is a modified 19–norprogesterone (fig. 2). Norprogesterone is identical to progesterone except that the methyl group at the 19 position is absent. Norgestomet has two other modifications: the presence of a methyl group at the 11 position and an acetate at the 17 position. Acetate has been added to provide longer half life in situ (Sinkula 1978). Norgestomet is me-

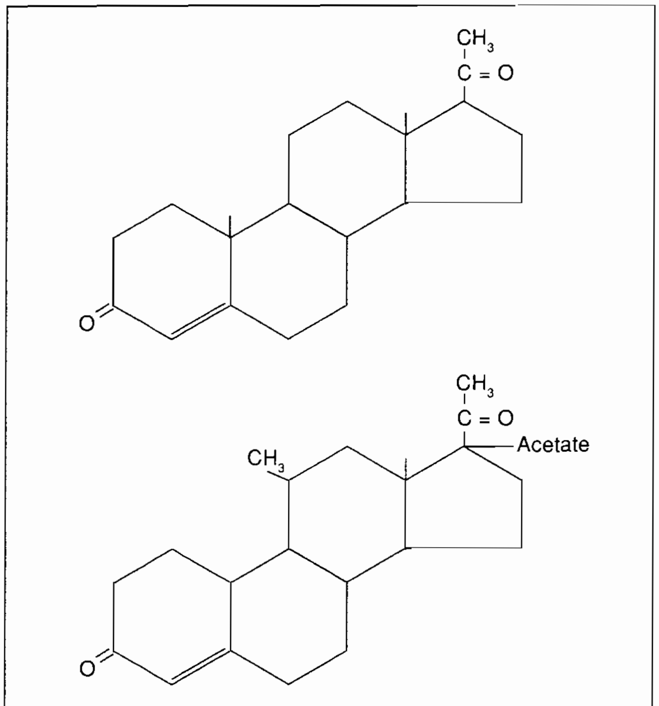

Figure 2. Chemical structures of progesterone (top) and norgestomet (bottom). Norgestomet is a norprogesterone (exactly like progesterone except the methyl group at the 19 position is absent). Two other differences from progesterone are that norgestomet has an acetate at the 17 position (in order to increase half-life in vivo), and a methyl group is included at the 11 position.

tabolized quickly (Moffatt et al. 1993) and is excreted in the urine and feces (Searle 1982). In both urine and bile, most of the excreted metabolites are highly polar materials demonstrated to have only about 4 percent of the progestational activity of norgestomet in the Clauberg assay (Searle 1982).

Norgestomet is a highly biologically active progestin. Gilbert et al. (1974) demonstrated that norgestomet is 15 times more biologically active than progesterone when orally administered to rabbits and 216 times more biologically active than progesterone when subcutaneously administered to estradiol–17β-treated mice. Wishart (1972) demonstrated that 140 µg of norgestomet and 45 mg of progesterone were required to suppress estrus in all treated heifers (which means that norgestomet is 321 times more potent than progesterone in this model). These data, combined with the data of Zimbelman and Smith (1966), would suggest that MGA is 90 times more potent than progesterone. This minimal dose of norgestomet required to suppress estrus in cattle was confirmed with silicone implant delivery of norgestomet by Machado (1994) and Machado and Kesler (1996). In their studies, 6-mg and 8-mg silicone implants were administered to cows for 16 days. None of the cows with 8-mg implants were detected in estrus with implants in situ. The smallest daily dose of norgestomet released by these implants was 136 µg, which occurred on day 16. However, in three cows with 6-mg implants, estrus was detected the first day after implant secretion dropped below 136 µg/day. Although this represents only 16 percent of the treated cows, 100-percent efficacy of estrus suppression was lost.

Norgestomet's principal mode of action for estrus synchronization is by suppressing estrus. Further, norgestomet has the progesterone biological activity to maintain pregnancy in ovariectomized heifers (Favero et al. 1990; Kesler, in press). Favero and coworkers demonstrated that norgestomet would maintain pregnancy from day 10 through parturition. Upon removal of the norgestomet implants, parturition (if the implants were removed at term) or abortion (if the implants were removed at midgestation or earlier) occurred within 52 hours. Therefore, norgestomet is as effective as progesterone (but at a substantially reduced dosage) for two of progesterone's main biological actions: estrus suppression and pregnancy maintenance.

Progesterone also has a role in regulating luteinizing hormone (LH) and subsequent follicular growth and maturation. Experiments utilizing the commercial hydron (polyethylene glycomethacrylate; Short 1975) norgestomet implant (6 mg) have demonstrated that, when it was implanted during pro-estrus, the dominant follicle present was maintained for the duration of the treatment, and there was no growth of medium or small follicles (Rajamahendran and Taylor 1991). Systemic estradiol concentrations were also elevated, and there was insufficient progestin activity to maintain a strong negative feedback on LH pulse frequency in a manner comparable to that of the luteal phase of a normal estrous cycle (Savio et al. 1993).

Rajamahendran and Taylor (1991) suggested that this implied that the norgestomet treatment given during pro-estrus mimics the actions of low concentrations of progesterone. This time period is, in fact, a time of low norgestomet secretion by the hydron implant (Kesler et al. 1995), and, therefore, obtaining a low progestin effect would be expected. In fact, when implants were changed during the persistence of the dominant follicle, LH pulse frequency decreased, estradiol concentrations decreased, and follicular atresia occurred (Savio et al. 1993). Therefore, when given in appropriate amounts, norgestomet was effective in provoking the progestinlike negative feedback on LH pulse frequency and on follicular atresia.

These conclusions were supported by Butcher et al. (1992), who reported that daily injections of 100 mg were was required to elevate systemic progesterone concentrations to levels of the luteal phase (5 to 7 ng/mL). In contrast, daily injections of only 45 mg were required to suppress estrus in all treated animals (Wishart 1972). The dosage selected for the norgestomet implant was based on the minimal quantity required to suppress estrus.

Administration of norgestomet on days 5–21 of the estrous cycle had no effect on progesterone secretion by corpora lutea (Domatob et al. 1994) and no negative effects on the establishment of pregnancy (Favero et al. 1993 and 1995, Machado 1994, Kesler et al. 1994). In order to assess the effect of norgestomet on early corpora lutea function and development in bovines, norgestomet was administered on days 1, 2, 3, and 4 after estrus (2 cows/day). The implants were left in situ for 12 days. In all eight cows, development of the corpora lutea, secretion of progesterone, and length of the estrous cycle were unaffected by norgestomet treatment. Therefore, negative feedback of norgestomet during met-estrus and di-estrus did not disrupt corpora lutea development or function (Kesler, unpubl. data).

It has been reported that norgestomet has a higher binding affinity to bovine uterine receptors than progesterone (Moffatt et al. 1993). Interestingly, however, although norgestomet has a higher binding affinity to bovine receptors, it did not bind (less than 0.1-percent cross-reactivity) to highly specific anti-progesterone immunoglobulin G developed in rabbits (Kesler et al. 1990). Norgestomet exhibits only a weak ability to competitively bind bovine endometrial glucocorticoid receptors (Moffatt et al. 1993). Although norgestomet does not interact with endometrial estrogen receptors, it exhibits weak estrogenic activity when tested in an estrogen-dependent stimulation of human breast cell test. However, to provoke estrogen stimulation, a dose of at least 100 mg of norgestomet given at one time would be required (Moffatt et al. 1993).

Norgestomet Safety

To obtain FDA approval for its use in cattle, investigators conducted numerous studies to establish norgestomet's safety in both the treated animals (cattle) and humans (Searle 1982). For cattle, studies were conducted with doses up to 60-fold excess to the recommended dose (6 mg implants). Daily observation of animals indicated no adverse reactions. Further, postmortem evaluation of the thoracic and abdominal viscera indicated that norgestomet caused no adverse effects.

To evaluate human safety, researchers conducted several studies in both monkeys and rats (Searle 1982). The study conducted in monkeys was designed to evaluate the human oral contraceptive effect of norgestomet. Oral treatment of 30 and 100 µg/kg (but not 0 and 10 µg/kg) per day increased the length of menstrual cycles, decreased the ovulation rate, and decreased the number of cycles during the 84-day treatment period. Throughout the treatment period, the only remarkable effect was amenorrhea, which was observed in five of six and three of six monkeys orally administered daily doses of 30 or 100 µg/kg, respectively. Further, when norgestomet was administered at these doses, the conception rate was depressed to zero. The 10 µg/kg of norgestomet per day had no significant effects on menstrual cycle length, ovulation rate, amenorrhea, or conception rate (Searle 1982).

For the rat studies, norgestomet was administered orally by gavage to two generations of rats at daily doses of 0, 0.0001, 0.001, 0.01, 0.1, or 1.0 mg/kg (Searle 1982). Administration of all doses produced no clinical signs indicative of toxicity. Weight gain was affected slightly only in the second-generation rats treated at the 1.0 mg/kg daily dosage. Also, in these same second-generation rats, fertility was slightly lower when compared to that of controls. There were no gross or histologic (adrenals, pituitary, and sex organs) changes that could be attributed to treatment with norgestomet. Absolute and relative organ weights from the treated groups were not different from the controls, although there was a slight decrease in liver weights in all treated animals.

In published resynchronization studies where norgestomet was administered during pregnancy, 158 pregnancies have resulted (Favero et al. 1993 and 1995, Machado 1994, Kesler et al. 1994, Domatob et al. 1997). No adverse effect of any kind has been observed. Therefore, the administration of norgestomet does not appear to affect embryonic or fetal development. However, as previously noted, norgestomet will inhibit parturition and therefore should not be inadvertently administered to pregnant animals where the implant is not going to be removed before parturition (Favero et al. 1990; Kesler, in press).

Contraceptive Efficacy

One study of norgestomet's contraceptive efficacy in deer was completed in 1995 (Jacobsen et al. 1995), and another was more recently published (DeNicola et al. 1997). Jacobsen's study was conducted in confined black-tailed deer. This study included 10 deer of which 7 were treated with 42-mg norgestomet implants approximately 1 month before the breeding season. In addition to the 10 female deer, 2 fertile males were included in the same confined area. Observations were collected over a 2-year period after treatment.

Subsequent to treatment, all of the treated female deer failed to exhibit estrous behavior. Further, males exhibited neither intentional pursuit, courting, nor tending bond behaviors toward treated females. After the first breeding season, all three control deer fawned, producing two sets of twins and one set of triplets. None of the seven treated deer fawned. All of the 10 female deer exhibited estrous behavior the next breeding season, and all 10 conceived.

Although this study utilized a small sample, additional studies with white-tailed deer (DeNicola et al. 1997) confirm the contraceptive effect of the 42-mg norgestomet implant. In addition, a contraceptive effect with similar efficacy to that of the 42-mg implant has been demonstrated with a 21-mg norgestomet implant (DeNicola et al. 1997).

The desired duration of contraception is controversial. Some groups encourage lifetime sterilization; others suggest that contraceptives should be reversible. The needle-less norgestomet implant was designed, as data confirmed, to be a 1-year contraceptive. Therefore, after 1 year of reducing the deer population, a decision can be made regarding how to control it in subsequent years.

Release from the 42-mg implant has been evaluated. This was accomplished by utilizing a validated in vitro system that mimics in vivo secretion (Kesler et al. 1995). Implants were evaluated daily over a 4-month period. The release of norgestomet from the implants was in a typical linear declining fashion (see figs. 3 and 4; Kesler et al. 1995). The best fit line was determined by correlating daily norgestomet released *v.* the log of day in vitro. This produced a correlation coefficient of –0.996. The maximal release of 638 µg was on the first day. During the first 3 months, more than 136 µg of norgestomet was released daily. This is a quantity that, as described earlier, suppresses estrus in cattle. The amount of norgestomet released daily thereafter decreased linearly. Based on the best fit release, norgestomet was released from the implant for 252 days.

For practical reasons, emphasis was placed on developing a contraceptive for the female deer. However, the contraceptive effects of progestins in males have been known for some time (Liskin and Quillin 1983). To assess the usefulness of norgestomet in male animals, researchers conducted a preliminary study to evaluate its effects on fertility-related factors in male rats.

This study included six males rats that were 12 weeks old at the onset of the experiment. Three rats served as controls and received no treatment. The other three rats were each administered one 6-mg silicone implant. At the end of 9 days, the implants were removed and replaced with new 6-mg silicone implants. This cycle continued for 63 days (7 implants/rat—9 days/implant). On day 63, all six rats were killed and trunk blood was collected. The plasma was analyzed for testosterone concentrations via a validated ELISA (Kesler et al. 1990). In addition, testes were collected and weighed. Mean individual testis weight of the norgestomet-treated rats was reduced ($P < 0.01$) and was only 37 percent of the control rats' mean testis weight (table 2). Mean testosterone concentrations in the plasma of norgestomet-treated rats were only 15 percent of the control rats' testosterone concentration. Although not highly significant ($P = 0.19$), norgestomet clearly had a biological effect on testosterone concentrations. A high level of significance ($P < 0.05$) was not achieved because the untreated rats demonstrated significant variability in their testosterone concentration and because so few animals were included in this prelimi-

Table 2. Mean testosterone concentrations and testes weights of rats treated with norgestomet.

Item	Control	Treated
Number	3	3
Mean individual testis weight	2.08 g	0.76 g[1]
Mean testosterone concentrations	4.54 ng/mL	0.66 ng/mL[2]

[1] Differs from the control group at the 0.01 level of significance.

[2] Differs from the control group at the 0.19 level of significance.

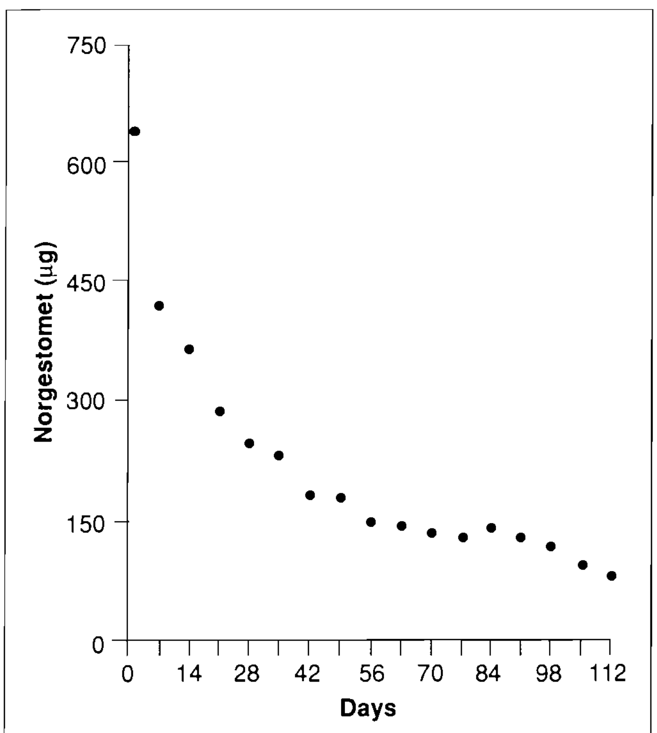

Figure 3. Actual daily in vitro release of norgestomet. Daily observations were collected; however, only weekly observations are illustrated.

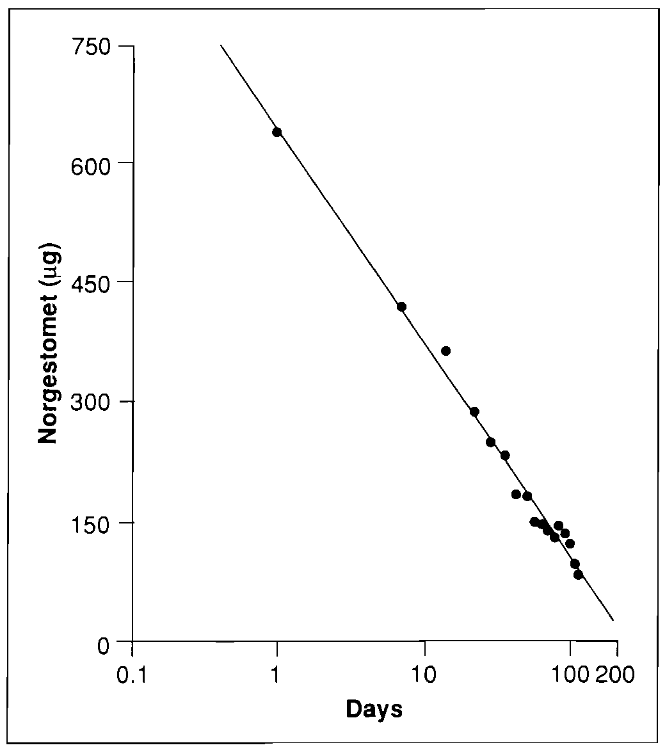

Figure 4. Daily release (with days converted to log of days) in vitro of norgestomet. Daily observations were collected; however, only weekly observations are illustrated. The regression equation is $Y = X(-265.26) + 637.23$ with Y = norgestomet concentration [µg] and X = log of days ($r = -0.996$; $P < 0.01$).

nary study. However, the three norgestomet-treated rats had the three lowest concentrations of testosterone in their plasma.

Collectively, these data suggest that norgestomet may have a contraceptive effect in males. However, these studies were conducted with high concentrations of norgestomet and not in deer. Further investigations evaluating sperm concentrations in the epididymis of male deer or in their ejaculate are needed.

Remote Needle-Less Delivery

Delivery of contraceptives to free-roaming animals is critical to successfully suppressing reproduction. The idea contraceptive should (1) be capable of being delivered remotely, (2) not pollute the environment, and (3) allow control such that only animals intended to be treated are treated and that the drug is handled and dispensed properly.

The norgestomet implants used in the deer efficacy studies were needle-less implants (fig. 5) that could be delivered at distances up to 40 m from the target animal (DeNicola et al. 1996). The needle-less implants have two major components. Their outer shell is manufactured from food-grade biodegradable and biocompatable chemicals. The components are already approved as food additives; even if all of the implant remained in place at the time of slaughter and was eaten by humans, that would not pose a hazard (U.S. Government 1993). The outer biodegradable shell is 0.635 cm in diameter and 2 cm long. The second component is the norgestomet manufactured in a matrix silicone implant. The silicone matrix is 0.42 cm in diameter and 1.4 cm long. It weighs 215 mg, of which 42 mg (19.5 percent) is norgestomet. The outer shell combined with the silicone/norgestomet weighs about 880 mg.

The needle-less implants are propelled via a compressed-air delivery system. For the 1995 study (Jacobsen et al. 1995), the needle-less implants were delivered at 26,152 cm/second (858 feet/second) producing 3.07×10^5 g-cm (22.15 foot-pounds) of kinetic energy. This system was designed for use in cattle, whose skin is far thicker than that of deer (Kesler and Favero 1997). Propelling the implants with that much kinetic energy caused trauma in deer (Jacobsen et al. 1995).

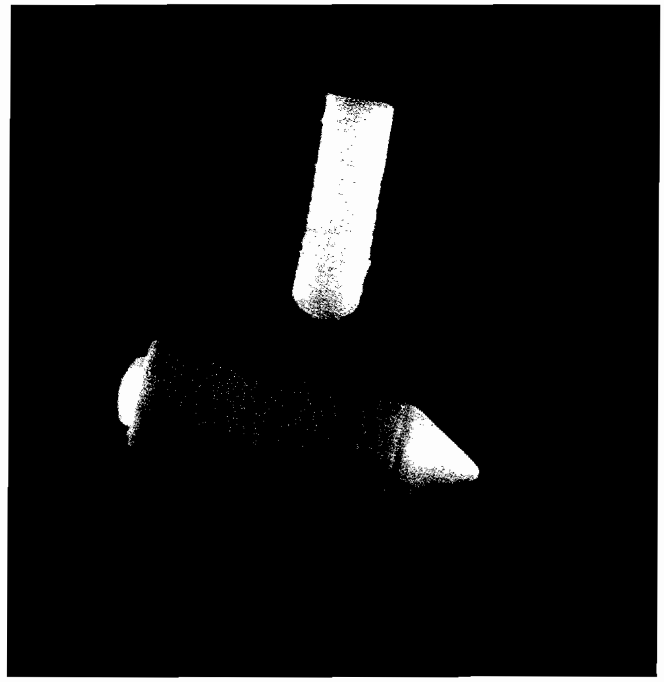

Figure 5. The needle-less norgestomet implant used in the deer studies. The photo shows the outer biodegradable shell (0.635 cm in diameter and 2 cm long) and the inner silicone matrix norgestomet implant (0.42 cm in diameter and 1.4 cm long).

Jacobsen's coworkers administered the needle-less implants in biceps femoris or semitendinosus or semimembranosus muscular at a distance of 3–30 m. Upon contact, deer exhibited one of two reactions: fleeing response without any apparent change in gait, followed by standing and grooming of the administration site, or immediate carriage of the hindlimb and lack of attempted weight bearing for variable durations.

In subsequent studies, the needle-less implant has been delivered with far less kinetic energy. Using less kinetic energy does not compromise the accuracy but significantly reduces the trauma in deer (DeNicola et al. 1997). In fact, when needle-less implants can be delivered silently, deer have minimal reaction to their delivery. In one study where cortisol concentrations were monitored to evaluate stress caused by the needle-less implant, they were not increased (Kesler, unpubl. data).

Upon contact with the skin, the needle-less implant first causes it to stretch (Gould 1984). After stretching, the implant penetrates the skin by producing a slit in it. After penetration has occurred, the skin then contracts back to almost its original form, with only a small slit left behind. The entry slit is shorter than the diameter of the projectile. Minimal, if any, bleeding occurs after penetration. Scab formation follows (Willis et al. 1994, DeNicola et al. 1996). The projectile does not carry a portion of the animal's hide into the wound but leaves behind only a small, raised welt on the skin at the point of projectile entry (Drake and Paul 1976, Kesler et al. 1989a).

Upon entry into living tissue, the outer shell dissolves in vivo in approximately 6 hours. I conducted both in vitro and in vivo studies to determine dissolution of the outer shell (table 3). The matrix silicone implant, although biocompatable and nonirritating, remains and delivers norgestomet by Fick's first law of diffusion as long as there is norgestomet contained within the silicone. By design, two deer that have been remotely treated with needle-less norgestomet implants were killed (about 2 months after treatment), and investigators examined the administration sites and musculature. In both cases, the norgestomet–silicone implant was recovered. Surrounding tissue was normal (DeNicola et al. 1996).

This remote delivery system is unique and has many advantages over all other delivery formats. Another remote delivery system utilizes syringe darts. Although syringe darts provide remote delivery, a nondegradable syringe and needle remain in the environment. Another remote delivery system being proposed utilizes genetically engineered viruses which provides no or very minimal control on its spread (Morell 1993, Wagner et al. 1994).

Table 3. In vitro and in vivo dissolution of the biodegradable shell of the needle-less norgestomet implant

Hour	Percent of implant dissolved	
	In vitro[1]	*In vivo*[2]
0	0	0
1	40	—[3]
2	70	—
3	90	—
4	95	—
5	98	[4]98.25
[5]6.39	100	—
24	—	[6]100

[1] In vitro conditions consisted of suspending the implant shell in 100 mL of phosphate buffered saline (pH 7.0) at 37 °C.

[2] In vivo conditions consisted of subcutaneously implanting the implant shell in rabbits. At 5 and 24 hours after implantation, eight rabbits (four each time) were killed to determine the amount of implant shell remaining.

[3] No observations were collected for times marked —.

[4] At 5 hours after implantation, approximately 2 percent, 0 percent, 3 percent, and 2 percent of the implant was remaining.

[5] The implant shell had completely dissolved at 6.08, 6.42, and 6.67 hours after placing the implants in solution.

[6] At 24 hours after implantation, no intact implants were present in any of the four treated rabbits.

Government Regulations

It is not the purpose of this article to review government regulations; however, it is important to make a few important comments. First and foremost, the norgestomet–silicone contraceptive reported herein is not approved for use by FDA. An Investigational New Animal Drug (INAD) authorization has to be granted to conduct the experiments reported. FDA has required that these studies be conducted only on confined animals and that they do not escape in such a way that they could enter the human food chain. Although approved in cattle, norgestomet is not approved for widespread use in deer. Before that approval is possible, a sponsor much accomplish numerous tasks (table 4) to ensure that the product is efficacious and safe not only to the treated animals but also to the humans that may consume treated animals. It is my opinion that this product can be approved by FDA.

Table 4. Information required to be submitted to the FDA's Center for Veterinary Medicine when requesting approval for the marketing of a new animal drug product (Center for Veterinary Medicine 1994)

1. Identification
2. Table of Contents and Summary i. Chemistry ii. Scientific rationale and purpose
3. Labeling i. Label identification ii. Nonprescription labeling iii. Prescription labeling iv. Use restrictions v. Medicated feed labeling vi. Draft labeling
4. Components and Composition i. Components ii. Composition iii. Fermentation of drug substance
5. Manufacturing Methods, Facilities, and Controls i. Manufacturer ii. Personnel iii. Facilities/equipment iv. New drug substance synthesis v. Raw material control vi. Manufacturing instructions vii. Analytical controls viii. Lot control number xi. Container x. Stability xi. Additional procedures xii. GMP (good manufacturing practice) compliance
6. Samples
7. Analytical Methods for Residues
8. Evidence to establish safety and effectiveness
9. Good Laboratory Practice Compliance
10. Environmental Assessment
11. Freedom of Information Summary
12. Confidentiality of Data and Information in a New Animal Drug Application

However, requirements for distribution have yet to be accomplished.

Since animals treated with norgestomet would have their implant in situ during the hunting season, a legitimate concern is finding the answer to the question, what will happen to the people who consume such an implant in a treated animal? First, tissue studies demonstrate that minimal norgestomet residue exists in all treated cattle tissues except liver and kidney (Searle 1982). Second, in regard to consumption of an implant, the silicone is exceptionally durable. When placed in vitro in concentrated hydrochloric acid over a 3-day period, the polymer is unaffected. Therefore, complete breakdown and absorption of all remaining norgestomet (like the effect on compressed pellets) is extremely unlikely (or impossible). Further, implants incubated in 250 mL of 1 N hydrochloric acid (at 37 °C), to mimic the acidic conditions of the stomach, released the same amount of norgestomet as in plasma in vitro conditions. New implants incubated for 24 hours in plasma and 1 N hydrochloric acid released 638 µg and 648 µg, respectively (within 1.5 percent of each other). Therefore, consumption of an implant a few weeks after implantation would release less than the safe 10 µg/kg daily dose previously discussed in monkeys.

Summary

Progesterone, produced by the corpus luteum, suppresses estrus in deer and cattle. Synthetic progestins (melengestrol acetate and norgestomet) that suppress estrus in cattle are also effective in deer. Synthetic progestins that are effective contraceptives in humans, however, do not suppress estrus and are not effective contraceptives in deer or cattle. Steroidal compounds are often viewed negatively because of the diethylstilbestrol (DES) scenario, even though they are widely used by humans. DES became implicated as a carcinogen because large doses (50 mg/day) of DES given to pregnant women caused an increased incidence of cervical cancer in their daughters (0.14 to 1.4 cases per thousand exposures [Cheeke 1993]). Norgestomet evokes all progesteronelike actions but at a much reduced dosage. Further, there are no data available to indicate that this steroid poses a risk. In addition to the data reported herein, norgestomet has been used for over a decade in cattle without any reported problems to either the cattle or to the human consumption of meat from treated animals. The only known progestin potent enough to be manufactured in a remotely delivered needle-less implant and still be efficacious as a contraceptive is norgestomet. This contraceptive system was evaluated by a scientific committee for use in wild goats (Warren 1992). That committee gave the needle-less norgestomet the highest possible ratings for delivery, safety, and efficacy. All data support their conclusions. In fact, the committee rated the needle-less norgestomet implant as the best contraceptive for wild goats (Warren 1992). Based on all data available, the same conclusion can be reached for deer. I encourage further evaluation and support of the development of this contraceptive for use in deer.

Acknowledgments

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Considerations for Immunocontraception Among Free-Ranging Carnivores: The Rabies Paradigm

Cathleen A. Hanlon and Charles E. Rupprecht

The raging North American controversy over the reintroduction of wolves into the ecosystem of the greater Yellowstone National Park area exemplifies the emotive relationship between humankind and the Carnivora. What forces act in concert to portray this much maligned Order in unfavorable light? Control of free-ranging carnivore populations by *Homo sapiens* has been practiced for centuries as part of a pastoral lifestyle, with the intent of protecting one's own life and livelihood from becoming freshly killed prey in the onslaught from mammalian competitors. Traditionally, control is equated most commonly with population reduction through direct elimination of individuals (e.g., typically social canids or solitary large-bodied felids) via lethal means including shooting, poisoning, trapping, gassing of dens, and habitat modification (Lewis 1968, U.S. Department of Agriculture 1992). In addition to reducing direct predation upon domestic livestock (sheep and cattle losses alone in the United States are estimated in excess of $80,000,000 annually [U.S. Department of Agriculture, National Agricultural Statistics Service 1991]), other perceived beneficial aspects of free-ranging carnivore population reduction include conservation of endangered species, such as Australian marsupials, subject to predation by introduced European red foxes (Boyle 1994), conservation of otherwise "desirable" species (game fowl and wild ungulates), and the alleviation of objectionable human–carnivore interactions (Wynne–Edwards 1964). Today, such interactions range from local citizen complaints of seemingly frivolous or nuisance wildlife encounter—raccoon disruption of a backyard songbird feeder, bear vandalism at vacation homes, etc.—to significant global public health issues (such as animal bite from the stray dog) and related human mortality either directly from overt injury or indirectly from exposure to a plethora of zoonoses, such as rabies or echinococcosis (Beran 1994). Nevertheless, a "manageable" number of mammalian carnivores is clearly viewed as beneficial when they serve human desire for sport, pelts, companionship, etc. Moreover, sound ecological, economic, and ethical arguments weigh against sole reliance upon lethal mechanisms to resolve such conflicts. A comprehensive approach to conflict management, rather than a narrow focus only upon overt, uncompromising predator decimation, is a valid and potentially more sustainable strategy to manage human–wildlife conflicts. Can targeting and controlling carnivore proliferation resolve the dilemma and validate this premise of alternative, nonpernicious intervention?

Historically, control of mammalian reproduction has been primarily directed toward domestic companion animals and livestock. Contraception has typically consisted either of surgical neutering of individuals, hormonal manipulation of reproductive function, or simple physical separation of the sexes. While the neutering of feral cats has been suggested as an alternative to elimination (Zaunbrecher and Smith 1993), these techniques, which are suited for management of individual reproductive function, may only rarely be applicable to most free-ranging carnivore populations, given the constraints of diverse species distribution and abundance. In contrast, oral delivery of a contraceptive agent for reproductive control among wild carnivores may be more feasible; initial efforts were reported as early as three decades ago (Balser 1964).

The observation of naturally occurring antisperm antibodies in a small proportion of humans has generated interest in the recruitment of the immune system for reproductive modulation (Aitken et al. 1993). Some postulated advantages of immunologically mediated contraception may be (1) economical vaccine production by recombinant techniques, (2) ease of administration, (3) relatively few side effects, and (4) a higher degree of biological specificity than traditional chemical drug delivery, which may have a broader phylogenetic and physiological spectrum of activity. From an ecological perspective, one potential advantage of wildlife immunocontraception would be to minimize deleterious effects of free-ranging carnivores by reducing or stabilizing total numbers, while avoiding vacant niches inherent to lethal reduction. A nonreproductive adult would inhibit ingress of new, fully reproductive individuals from surrounding areas (Porter et al. 1991). Arguably, one weakness of the immunocontraception prospectus is individual variation in the immune response, which may lead to unpredictability regarding the duration and magnitude of effect in a particular animal. However, if a measurable effect among a local population is achieved, some variation among individuals may be acceptable.

Typically, oocyte and sperm antigens are sufficiently compartmentalized so that an immune response is not normally elicited; however, these antigens are clearly immunogenic (Haimovici et al. 1992, Liu et al. 1990). In this regard, considerable research has focused on zona pellucida (ZP) antigens (Kirkpatrick et al. 1991 and 1992, Hasegawa et al. 1992, Jones et al. 1992). Despite a highly species-specific interaction between the sperm surface and a glycoprotein component of the ZP, antibodies to the ova of one species inhibit in vitro and in vivo fertilization of another species (Aitken et al. 1993). An unexpected finding from ZP immunization has been the delayed cessation of ovarian cycling from destruction of primordial follicles or essentially induced premature menopause in animal models (Hasegawa et al. 1992, Jones et al. 1992), another potential drawback in the implementation for wildlife.

Alternative approaches have focused upon inducing antibodies to the cumulus oophorus of the conceptus (Tesarik et al. 1990) or disrupting regulatory hormones such as human chorionic gonadotrophin, gonadotropin-releasing hormone, luteinizing hormone-releasing hormone, and follicle-stimulating hormone (Aitken et al. 1993). Additionally, while still the subject is still in the early stages of investigation, some promising results have also been obtained with disruption of spermatogenesis (Grubb 1991). Some of these methods raise complex medical or ethical issues, for human reproductive manipulation because the end result may be essentially abortifacient or complications related to immune-complex formation. Whether these matters would be equally as controversial when applied to a "nuisance" carnivore species has yet to be determined. However, it should be clear that absolute restriction to the species of interest would be optimal.

Other suggested interventions would target levels of reproductive hormone (testosterone or progesterone) directly (Linhart 1964, Linhart et al. 1968, Awoniyi et al. 1992, Moudgal et al. 1992, Talwar et al. 1992, Vanage et al. 1992, Deshmukh et al. 1993, Dowsett et al. 1993, Ladd 1993). The significant limitation of this approach in a free-ranging carnivore population is the potential for an undesirable effect upon sexual behavior, social interactions, and hierarchy (Awoniyi et al. 1992, Moudgal et al. 1992, Dowsett et al. 1993).

To date, no species-specific reproductive antigens have been identified, although unique contraceptive antigens for humans (Aitken et al. 1993), wolves (U.S. Department of Agriculture 1992), red foxes, rabbits, kangaroos (Morell 1993), deer (Porter et al. 1991), wild swine (Fletcher et al. 1990), and many others (Wynne–Edwards 1964), would be of great utility. The apparent conservation of many reproductive antigens among mammalian groups raises the undesirable, even detrimental, potential to unintentionally affect nontarget species, possibly including humans, valuable domestic animals, endangered or threatened wildlife, and nonnuisance carnivore species. In lieu of species-specific antigens, a species-specific vector (plasmid DNA, viral, bacterial, etc.) would be a potential strategy to limit the contraceptive effect solely to the target species. Unfortunately, such carnivore species-specific vectors have also yet to be identified.

The physical delivery of a desired contraceptive may consist of a variety of singly applied or combined approaches. For example, live-trapping of free-ranging carnivores and direct inoculation of a contraceptive may be of some value, particularly in areas where high human–carnivore interaction is problematic and necessitates a response, but complete elimination of carnivores is not desired by human residents, and lethal control is unacceptable. Except for under these limited conditions, the labor-intensive nature of this approach and the poor capture rates of some carnivore species may render this method largely impractical.

Conversely, injection of contraceptive agents may be achieved remotely via a blow gun, dart gun, or similar device. This is currently a procedure in progress for an insular population of feral horses off the eastern mid-

Table 1. Oral vaccination of carnivores with recombinant viruses

Agent	Species (common name)	Reference
Vaccinia-Rabies Glycoprotein Recombinant Virus		
Family Canidae	*Vulpes vulpes* (red fox)	Blancou et al. (1986)
	Canis lupus (domestic dog)	Blancou et al. (1989)
	C. latrans (coyote)	Artois et al. (1990)
	Alopex lagopus (arctic fox)	Chappuis and Kovalev (1991)
	Nyctereutes procyonoides (raccoon dog)	Chappuis and Kovalev (1991)
	Urocyon cinereoargenteus (grey fox)	Rupprecht et al. (1992a)
Family Felidae	*Felis domesticus* (domestic cat)	Blancou et al. (1989)
	Lynx rufus (bobcat)	Rupprecht et al. (1992a)
Family Mustelidae	*Mephitis mephitis* (striped skunk)	Tolson et al. (1987)
	Mustela putorius (ferret)	Brochier et al. (1988)
	Meles meles (European badger)	Brochier et al. (1989)
	Lutra canadensis (river otter)	Rupprecht et al. (1992a)
	Mustela vision (mink)	Rupprecht et al. (1992a)
Family Procyonidae	*Procyon lotor* (raccoon)	Wiktor et al. (1985)
Family Ursidae	*Ursus americanus* (black bear)	Rupprecht et al. (1992a)
Raccoonpox-Rabies Glycoprotein Recombinant Virus		
Family Procyonidae	*P. lotor*	Esposito et al. (1988)
Family Canidae	*C. lupus*	Esposito et al. (1992)
	U. cinereoargenteus	Esposito et al. (1992)
Family Felidae	*F. domesticus*	Esposito et al. (1992)
	L. rufus	Esposito et al. (1992)
Family Mustelidae	*M. mephitis*	Fekadu et al. (1991)
Human Adeno(5)-Rabies Glycoprotein Recombinant Virus		
Family Procyonidae	*P. lotor*	Charlton et al. (1992)
Family Canidae	*V. vulpes*	Charlton et al. (1992)
	C. lupus	Campbell (1994)
Family Mustelidae	*M. mephitis*	Charlton et al. (1992)
Baculo-Rabies Glycoprotein Recombinant Virus		
Family Procyonidae	*P. lotor*	Fu et al. (1993)

Atlantic shore (Kirkpatrick et al. 1991 and 1992). As above, this approach is also largely limited by species secretiveness, tolerance for humans, the accuracy of the operator, and the ability to identify previously inoculated individuals.

Given these limitations, additional methodologies may have to be considered for long-term, widespread carnivore reproductive control. For example, the effectiveness and relative ease of using baits to deliver a biological, rather than lethal chemicals as practiced historically, to wild carnivores has been demonstrated, principally through the wildlife rabies vaccination of several reservoir species in Europe and North America (Johnston et al. 1988, Bachmann et al. 1990, Brochier et al. 1990, Rupprecht et al. 1992a, Winkler and Bogel 1992, Campbell 1994). This example of wildlife rabies vaccination has often been cited over the last decade to document the degree of sophistication achieved in reaching free-ranging carnivore populations. To date, these field systems involve either modified live rabies viruses or recombinant orthopoxvirus vectors that undergo limited replication without perpetuation or apparent adverse effect (at least in the latter viral scenerio) in the targeted host. The advantages of a self-replicating entity are economy and the more reliable induction of an immune response without the need for multiple doses or adjuvants. Moreover, vectors with wide carnivore host susceptibility (table 1) are advantageous with a disease such as rabies, in which the pathogen is not restricted to a single narrow host niche. For example, a single biologic may be useful for control of rabies in raccoons, red foxes, and coyotes in various geographic areas where rabies strains are perpetuated by different carnivore species. Yet this same precept of broad application may be counterproductive without species-specific expression products, when the effect is immunocontraception in co-occurring species, rather than simply rabies vaccination.

In addition to live virus vaccination, successful oral immunization of raccoons in captivity has also been demonstrated with a baculo–virus system, in which rabies glycoprotein expression in an insect cell culture resulted in sufficient quantities of antigen to immunize animals directly by mouth (Fu et al. 1993). Similarly, raccoons and other carnivores may be orally immunized with inactivated viral preparations (Rupprecht et al. 1992b). While the amount of antigen required may be economically prohibitive given current production limitations, the concept offers a choice avenue of investigation that departs from the traditionalist approach toward a replicative vector, if a restricted reproductive antigen were available.

A self-replicating biologic has an inherent potential for adverse effects that is influenced by host variables, such as species and individual age, immune status, concurrent infectious or metabolic conditions, etc. The latent risk for adverse effects may be nearly immeasurable under traditional laboratory or field conditions. These concerns are particularly relevant to an immunocontraceptive, self-replicating biologic destined for free-choice broadcasting and consumption. While the occurrence of immunocompromised hosts at risk for vaccine exposure may be remote, any self-replicating vector, even a highly attenuated virus, presents increased risks in such a host (Fenner et al. 1988, Hierholzer 1992).

The immunocompromised host scenerio has led to the development of functional animal models. Bosma and Carroll (1991) have identified a single gene mutation in mice that results in the inability to form functional B and T cells in homozygotes. Lacking the capacity for a specific immune response to pathogens and commensal organisms alike, severe combined immunodeficient (SCID) mice must be housed under aseptic conditions in a pathogen-free environment. An inheritable, functionally similar condition occurs in humans. Thus, the SCID model may be particularly useful in the elucidation of events during recombinant viral infection and may contribute toward the knowledge of the overall biosafety of these new biologics (Hanlon et al. 1997). Additionally, such studies may identify critical components of a prophylactic regimen, should adverse effects occur in an immunocompromised host. As a more sophisticated working knowledge of viral genetics is gained, genomic sequences crucial for replication in a particular host may be targeted and eliminated (Tartaglia et al. 1992a and b), increasing species specificity, as well as overall biological safety.

The synergism provided by vaccine vector, bait type, and distribution parameters (density, method, spatiotemporal factors) should ultimately maximize target species contact and minimize nontarget species uptake of a given biological. However, it is difficult to imagine total vaccine restriction to a single carnivore population even under ideal circumstances. Many bait studies have previously demonstrated an effect on species other than the target and implications for nontarget groups, such as domestic animals, humans and nonmammals, despite the original application and intention (Ballantyne and O'Donoghue 1954, Linhart 1964, Lewis 1968, Westergaard 1982, Bachmann et al. 1990, Fletcher et al. 1990, Trewhella et al. 1991). For example, a decade of applied research toward development of a prototype delivery device for oral raccoon rabies vaccination (Rupprecht et al. 1987) in the Eastern United States, resulted in a fishmeal–polymer bait that was readily consumed by a majority of raccoons under laboratory and field conditions (Rupprecht et al. 1992a). Yet variations in bait density (10–100/ha), distribution season, habitat type (barrier island to forested uplands), or method (hand delivery *v.* aerial), targeting ecotones suggestive of high raccoon activity, were unable to exclude consumption by other mammals (Hanlon et al. 1989 and 1993, Hable et al. 1992, Rupprecht et al. 1992a). Viewed as

Table 2. Biomarker[1] detection in nontarget species from fishmeal–polymer bait consumption: Virginia, Pennsylvania, and New Jersey (1990–93)

Species	No. positive/total	Percent
Opossum *(Didelphis virginianus)*	64/95	67
Striped skunk *(Mephitis mephitis)*	13/32	41
Domestic cat *(Felis domesticus)*	6/20	30
Red fox *(Vulpes vulpes)*	2/6	33
River otter *(Lutra canadensis)*	1/5	20
Porcupine *(Erythizon dorsatum)*	3/36	8
Black bear *(Ursus americanus)*	2/198	1
Norway rat *(Rattus norvegicus)*	1/8	13
House mouse *(Mus musculus)*	2/15	13
Rice rat *(Oryzomys palustris)*	2/7	29

[1] Tetracycline analysis from mandibular bone as described by Hanlon et al. (1989).

a composite (table 2), utilization in excess of 100,000 V–RG vaccine-laden baits specifically for raccoons nevertheless demonstrated contact by a variety of other carnivores and a few rodent species (albeit extremely small numbers). Overall biomarker data indicated bait consumption by a limited variety and number of nontarget species with no evidence of consumption by certain others (such as white-tailed deer during hunting season). These results could not have been predicted a priori, without placebo baiting and nontarget species surveillance. Observed nontarget species outcomes from vaccine exposure in the field have ranged from no apparent effect to immunization. However, what does the bait contact rate of a nontarget, competitor species (e.g., opossums) imply, especially if it approximates or exceeds that of the target species [raccoons]? From a disease control perspective, in which no untoward effects have been demonstrated in the nontarget species at issue, the answer may range from simple nuisance to a resultant economic infeasibility, depending upon the degree of interference and the number of vaccine-laden baits not available to the intended species. Clearly, what looks like a trifling matter—say, an overabundance of opossums vaccinated against a given infectious disease—may not be trivial in regard to immunocontraception, in light of species-specific vectors, antigens, baits, etc. This nontarget species contact problem may figure prominently if the species in question is a keystone species.

Long-term results of applying free-choice oral immunocontraception to free-ranging carnivores (and the associated nontarget milieu) are impossible to predict at present with any reasonable degree of certainty, as regards either safety or efficacy. For example, the efficacy of oral rabies vaccination among a target population may be assessed by (1) confinement studies with baits followed by challenges, (2) capture of free-ranging animals from a vaccinated area for subsequent laboratory challenge (Rupprecht et al. 1993), (3) measurement of seroconversion among free-ranging animals in an area, or simply (4) surveillance for naturally occurring disease. However, the minimal acceptable levels of these assessment techniques that would predict successful disease control or elimination are not known a priori, nor from present data, nor for a variety of complex ecological settings.

A proportion of the population may not consume baits due to a variety of factors. Some heritable behavioral traits, such as temerity in consumption or total avoidance of novel items, like artificial baits, may play a role in the inability to reach a segment of the targeted population. It follows that a particular cohort with a behavioral trait of bait avoidance may gain a competitive advantage. The result would be increasing difficulty in reaching this remaining, actively prepetuating segment of the population via baits. This scenario may be particularly troublesome given the high reproductive capacity of some species. Additionally, because no vaccine is completely efficacious in all individuals, it may be possible to selectively favor nonresponders (the perceived "mangey" or "wormy" individuals), due to major histocompatibility restriction, inherited immunodeficiencies, or immunocompromising infectious agents (Nossal 1989). If these latter theoretical demes gain even a minor reproductive advantage within a population, they may eventually initiate or exacerbate disease and related conditions. Amplification of this particular component of a carnivore population may severely restrict genetic diversity, as in present day cheetah (i.e., *Acinonyx)* (Cohn

1986), and subsequently compromise the overall health and viability of the community at large.

To be ultimately successful, an immunocontraceptive control program will intuitively require reaching a majority of individuals; how can the ideal mix of gene frequencies be ensured in light of this seeming conundrum? At first consideration, a readily transmissible, "safe" recombinant agent (while a bane to regulatory authorities) might appear to overcome the limitation of inequitable bait uptake and biological response. Exposure to a readily transmissible vector could approach unity, successfully reaching all members of a particular carnivore population. But, as evidenced by the global emergence and entrenchment of canine parvovirus within domestic and wild canid populations (Parrish 1994), this strategy may have significant uncontrollable and potentially detrimental effects. Even if a so-called species-specific antigen were discovered, geographic containment of such a highly contagious agent could not be assured. How would programs aimed, for example, at red foxes in the New World prevent exchange to red foxes in the Old World, involvement of related subspecies, or spillover to kin in the same genus, given the frequency of transoceanic travel and exotic and endemic species translocations (Rupprecht et al. 1996)? Similar questions could be raised for other taxa—canid, mustelid, viverrid, etc.

In conclusion, incipient investigations toward immunocontraceptive population management are quite intriguing. Their development for free-ranging carnivores appears well motivated and potentially desirable, at first glance, for numerous applications, given the limitations of available alternatives to reconcile the human–predator interface problem. Nonetheless, it will be crucial to proceed from the outset in as prudent a manner as possible, given the above-voiced concerns. It will be necessary to address, in comprehensive fashion, the potential for untoward events, and objectively divest real from perceived risks, much akin to the scientific scrutiny directed toward recombinant biologics more than a decade ago. In concordance with the recommendations of the World Health Organization (1993) in their Consultation on Reproductive Control of Carnivores, future directions of immunocontraceptive research should include continued efforts to develop species-specific bait delivery techniques, and species-specific contraceptive effects, either through antigen or vector. Given these goals, future research would logically involve international, multidisciplinary, collaborative efforts, strongly based upon objective, testable hypotheses. Until then, free-choice broadcasting of nonrestrictive contraceptive biologics may be unconscionable due to, as yet, unpredictable, undesirable, and potentially far-reaching repercussions, not only in the target species, but also in critical nontargets that share this increasingly burdened and now readily traversed globe.

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Immunocontraceptive Vaccines for Control of Fertility in the European Red Fox *(Vulpes vulpes)*

Mark P. Bradley

Abstract: This paper describes the strategies being employed in the development of an immunocontraceptive vaccine using sperm antigens, to control fox populations in Australia. It is proposed that such a vaccine will be delivered orally in a bait, thereby ultimately stimulating a mucosal immune response within the female reproductive tract. The eventual success in producing such a vaccine requires the identification of gamete antigens that cause immunological infertility, a detailed understanding of the reproductive immunology of foxes, and the selection of the most effective form of antigen delivery system.

Keywords: Sperm antigens, immunocontraception, mucosal immunity

Introduction

Immunocontraception potentially offers the most effective method for the management and long-term population control of vertebrate pest species. The idea of using fertility control for such purposes is not new. In the early 1960's, a number of investigators examined the use of chemical sterilants to limit the reproductive capacity of animal populations (Linhart 1964). None of these methods proved effective, probably because these chemicals lead to castration of the target species. Castration removes the source of the key sex hormones, and this effect has the potential to interfere with the normal social structure of a target population, an undesirable outcome that could lead to a breakdown in established social hierarchies and may result in compensatory breeding.

Immunocontraception for Feral Species

In 1992, the Cooperative Research Centre for the Biological Control of Vertebrate Pest Populations was established in Australia to explore alternative methods of fertility control based on the use of gamete antigens as immunogens. One of the species being targeted in this research is the European red fox *(Vulpes),* which is a major vertebrate pest in Australian responsible for the loss of many native species through predation.

Our approach to immunocontraceptive control of the fox involves developing a bait-delivered oral vaccine. In this paper, I will discuss the experimental approaches used in the development of such a vaccine for foxes. Specifically, the focus will be on the identification of sperm antigens as vaccine candidates, the immunological questions that need to be addressed, and the development of appropriate delivery systems.

Although these considerations are directed toward an application for the fox, many of the concepts are relevant for immunocontraception in other species. The wider concerns relating to species specificity, and the use of recombinant vaccines, will be covered in the paper by Tyndale–Biscoe in this proceedings.

Components of an Immunocontraceptive Vaccine for Feral Species

A successful contraceptive vaccine should (1) block fertilization or early embryonic development; (2) affect both sexes; (3) be species specific; (4) provoke a prolonged and sustained immune response; and (5) not interfere with the normal social function of the animal. In particular, an effective mechanism for transmitting the vaccine throughout the target population must be found. This mechanism must be cost effective to manufacture and administer and must not impose hazards to the environment. These caveats make the development of an immunocontraceptive vaccine for wild animals highly challenging.

Reproductive Studies

Sperm Antigens as Targets for Immunocontraception

Vaccines developed toward sperm antigens would probably be capable of inducing infertility in both males and females. Potentially, this characteristic has the advantages not only of rendering sperm within the male genital tract incapable of fertilization before entry into the female but also of inactivating sperm within the female genital tract. The direct immunization of males and females with extracts of sperm or testis results in a significant inhibition of fertility (Menge and Naz 1988).

We have tested the antifertility effect of antibodies to sperm in a group of six female foxes (Bradley 1994). Necropsy results revealed that there were 21 ovulations in this group of foxes. In all females examined, no live fetuses were found; 13 of 21 oocytes had been fertilized and embryos implanted, but all failed as determined by the presence of embryonic resorption scars. Examination of uterine flushes failed to find any unfertilized or preimplantation embryos. It was concluded that immunization with sperm results in an immunological block to fertility and that sperm immunization has two effects, one at the embryonic level and the other during fertilization.

The results of this experiment are consistent with those previously reported on the effect of experimentally induced sperm antibodies on fertility (O'Rand 1977, Koyama et al. 1984). Many of these experiments found that anti-sperm antibodies appeared to exert their effect on fertility not at the level of fertilization but rather at later stages ranging from early blastocyst development to implantation (Menge and Naz 1988), suggesting that some antigens are shared between the sperm and the embryo. Immunization against such complex mixtures of antigens is not really a practical approach for vaccine development. Instead, the individual antigenic components capable of causing immunological contraception need to be identified. Indeed, a number of specific sperm proteins can impair fertility when used to immunize animals (Naz 1987, LeVan and Goldberg 1990).

The most common approach to sperm antigen identification and selection is the use of monoclonal antibodies to sperm protein of the species under study (Anderson et al. 1987). One of the best examples is the PH-20 protein originally identified with monoclonal antibodies to guinea pig sperm. Fertility trials have shown that male and female guinea pigs immunized with PH-20 become infertile (Primakoff et al. 1988). More recently, the PH-20 genes from a number of other species have been cloned, leading to the possibility that this antigen may have applicability as a vaccine target in other species.

Another sperm antigen of interest is SP-10. This has been designated as a "primary vaccine candidate" by the World Health Organization Task Force on Contraceptive Vaccines (Herr et al. 1990a and b). Antibodies to SP-10 inhibit the penetration of hamster eggs by human sperm, and trials in baboons currently in progress will assess the applicability of this antigen as an immunocontraceptive for humans. Recently, a homologue of SP-10 (called MSA-63) has been identified in the mouse and cloned (Liu et al. 1990). Furthermore, antibodies to MSA-63 have been shown to have a strong inhibitory effect on the in vitro fertilization of mouse ova, providing good support that this class of antigens is worthy of study as potential targets for immunocontraception.

Fox Sperm Antigens Currently Being Assessed for Use in an Immunocontraceptive Vaccine

A number of monoclonal antibodies have been developed to fox sperm antigens and used to clone the cognate genes from a fox testis cDNA library. One of these candidate antigens, FSA-1r, has been through fertility trial testing and found to have no effect on fertility. Other antigens are currently in the fertility trial phase of assessment.

Fox Acr.1 (Acrosomal Protein 1)

The FSA-Acr.1 protein is located within the acrosomal matrix of fox sperm, and it is first detected during spermatogenesis on the developing acrosome of round and elongating spermatids (Beaton et al. 1995). A monoclonal antibody to FSA-Acr.1 (FSA-10) was used to screen a fox testis cDNA library, and a cDNA clone was isolated. Database searches with the deduced amino acid sequence of FSA-Acr.1 revealed that the clone has high homology to both human and baboon sperm protein SP-10 and the mouse sperm protein, MSA-63. The region of highest homology is within the carboxyl terminus. Within the central portion of the open reading frame, the fox sequence contains amino acid motifs that are absent from both the human and baboon SP-10 and mouse MSA-63 sequences. We have expressed the FSA-Acr.1 protein in vitro, and this protein is being assessed in fertility trials to determine whether or not antibodies to FSA-Acr.1 can impair fertility.

Fox LDH-C_4

Lactate dehydrogenase C_4 (LDH-C_4) is an intracellular sperm-specific enzyme a portion of which is located on the sperm flagella plasma membrane. A number of studies have previously demonstrated that, when purified LDH-C_4 is used to immunize either mice, rabbits, or baboons, fertility was reduced by 60 to 80 percent (LeVan and Goldberg 1990). Epitope mapping studies of mouse and human LDH-C_4 have identified an antigenic peptide within the N-terminal region of the open reading frame, from amino acids 5–19 (Millan et al. 1987). This sequence also has the greatest variation in sequence between different species. We have recently cloned a fox LDH-C_4 cDNA and have derived sequence information from the 5' region of the open reading frame. This research has enabled us to synthesize a peptide to this region that was subsequently conjugated to the tetanus toxoid protein as an immunogenic carrier protein. This peptide-protein conjugate has been used to immunize female foxes by the intra-Peyers' patch route, and the immune responses and the effects of this immunization on fox fertility are currently being measured.

Fox PH-20

Cloning of the guinea pig PH-20 revealed that it has homology at the protein level with bee venom hylauronidase (Gmachl and Kreil 1993). Hylauronidase enzymatic activity is present within the head of mammalian sperm, and it has been shown that PH-20 has hylauronidase enzymatic activity (Gmachl et al. 1993). We have isolated a cDNA from a fox testis cDNA library encoding PH-20, and partial sequence analysis indicates close homology to PH-20 antigens cloned from other species. The antifertility effects in foxes of PH-20 immunization will be assessed with the whole protein and with selected peptide sequences.

Production of Recombinant Antigens

The in vivo testing of candidate antigens requires the large-scale production of recombinant proteins. A number of commercially available protein expression systems exist for this purpose; however, the selection of the system for a particular purpose eventually depends on the properties of the antigen under study. For example, is the protein highly glycosylated, and how important is this for antigenicity? Or, is the protein composed of multiple subunits? These considerations all have bearing on the success and selection of any one expression system. We have extensively used the maltose binding protein (MBP) expression system for the production of recombinant sperm proteins. This system produces a fusion of MBP to the protein of interest. Following expression, the fusion product is purified by affinity chromatography to yield a hybrid protein. The MBP can be cleaved and purified from the target protein, but this has some drawbacks in that small amounts of MBP still contaminate the antigen preparations, and loss of antigen occurs at each purification step. Unfortunately, the selection of expression systems for production of recombinant proteins is still something of a trial-and-error procedure, and several systems may have to be evaluated before selection of one that suits the purpose of the antigen under study.

In Vivo Fertility Testing of Recombinant Sperm Antigens

Ideally, during the selection of monoclonal antibodies that identify candidate sperm vaccine antigens, part of the testing procedure should include the use of functional assay to determine the effect of these antibodies on either sperm–egg binding or fertilization in vitro. While such assays are readily available for some species, researchers are limited in the fox in the routine use of such assays by both the biology of foxes and the paucity of an in vitro fertilization assay system. Because the fox is a seasonal breeder, the availability of gametes for such studies is restricted to 2 months every year, a fact that severely restricts the opportunity for assays. There is one reported study of attempts to establish an in vitro fertilization system for foxes. But, unfortunately, this procedure is still in the early experimental stages, and its routine application is not feasible at present (Farstad et al. 1993).

An alternative is to test the antifertility effects of candidate antigen(s) in vivo in female foxes. This approach is both time consuming and expensive, but it is highly informative. For example, we have routinely performed necropsies on the immunized foxes at about 40 days after mating to evaluate the biological implications of the immunization regime(s) on fox reproduction. At the same time, samples of reproductive-tract fluids are collected for assays of the immunoglobulin levels within each section of the tract. This approach provides information on both the immunology of the treatment and the in vivo effects on fertility.

Do We Use Proteins or Peptides as Vaccine Antigens?

Ultimately, the choice will have to be made as to whether a recombinant vaccine for immunocontraception is developed which contains the full target protein or an antigenic peptide. Decisions will have to be based on the considerations of the species specificity of the antigen and the ability of any selected peptide epitope to produce a sufficient immune response to block fertility. The success of ongoing research on the selection, design, and construction of peptide antigens will be vital for the future development of peptide-based vaccines.

Immune Responses to Gamete Antigens

Mucosal Immune Response in the Female Reproductive Tract

The use of a bait-delivered oral immunocontraceptive for foxes requires a detailed understanding of the processes involved in the induction, modulation, and duration of genital tract mucosal immunity. The immune responses within the female genital tract are similar to that observed at other mucosal sites. Vaginal and cervical secretions contain high levels of immunoglobulin A (IgA) that appear to be locally synthesized. It has previously been shown that the reproductive mucosal site is linked to the common mucosal system and that IgA plasma cells stimulated at a distant site, such as the gastrointestinal tract, can rapidly migrate to the female reproductive tract (McDermott et al. 1980, Parr and Parr 1989 and 1990).

Using a model recombinant-derived antigen, maltose binding protein (MBP), we have investigated different immunization regimes to determine which route induces reproductive-tract mucosal immune responses within female foxes. Direct administration of antigen into the Peyers' patches (IPP) has been used because this route effectively mimics the oral presentation of an antigen to the gut associated lymphoid tissue (Dunkley and Husband 1990). Peyers' patch immunization induces a mucosal immune response within the female reproductive tract, but in the absence of a booster immunization, the antibody responses are transitory, particularly for IgA (fig. 1). This fact indicates that maintenance of vaginal IgA antibodies may require the antigen to persist.

To examine this, an experiment was conducted to test the effect of secondary immunizations with MBP on the maintenance of vaginal antibody levels. Three female foxes were immunized IPP and then boosted intradermally (ID) 1 and 2 months later. The results show that the levels of both serum and vaginal antibodies were maintained at higher levels and for longer compared with foxes receiving a single Peyers' patch immunization (fig. 2). In light of this information, female foxes in fertility trials are now routinely immunized IPP followed by a secondary immunization ID, thus ensuring that high antibodies levels are present within the reproductive tract throughout the period of the fertility trial.

Immune Responses and the Endocrine System

A number of studies have demonstrated that the sex hormones estrogen and progesterone can influence immunoglobulin G (IgG) and IgA antibody production within the female reproductive tract (McDermott et al. 1980). Any immunocontraceptive vaccine strategy will have to address the effect that these localized

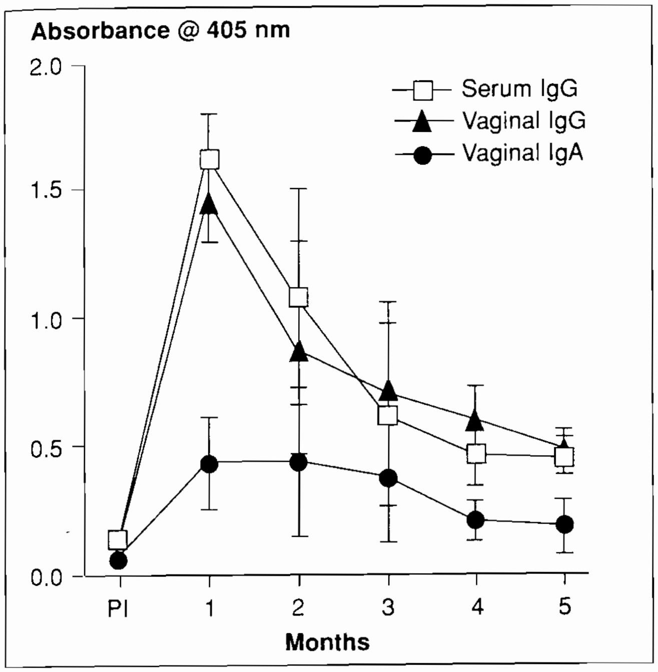

Figure 1. Serum and vaginal fluid antibody responses (Mean ± SD; $N = 3$) in female foxes as determined by enzyme-linked immunosorbent assay (ELISA). Each fox was immunized once with MBP into four Peyer's patches.

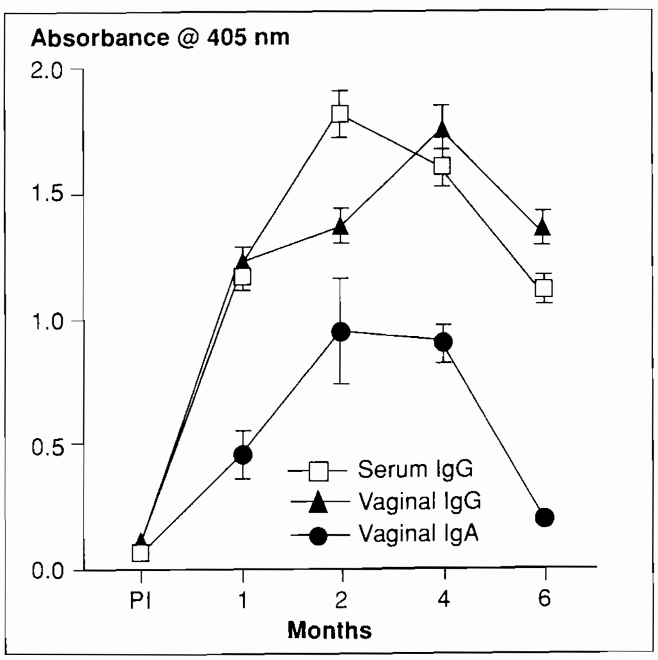

Figure 2. Serum and vaginal fluid antibody responses (Mean ± SD; $N = 3$) in female foxes as determined by ELISA after immunization with MBP into four Peyer's patches, followed by intradermal booster immunizations 1 and 2 months later.

changes in the immune status of females may have on immunocontraception. Effective immunocontraception will depend on the maintenance of high levels of antisperm antibodies within the oviducts, uterus, and vagina during mating. If changes in the localized antibody concentrations are substantial during this critical period, then contraception may be compromised (Wira and Sandoe 1987). Studies are under way in the fox to determine if localized changes are seen in the reproductive tract IgG and IgA during estrus.

Long-Term Maintenance of an Immune Response

A problem that may need to be addressed in the administration of an immunocontraceptive vaccine to an outbred fox population is the variability of the immune response between individuals. Effective application of a vaccine for fertility control requires that a high level of immunity be achieved among individuals exposed to the vaccine. It may, therefore, be necessary to include multiple antigenic determinants within a vaccine to stimulate a broad range of immune responses. In addition, the antigen(s) may need to be presented in conjunction with other highly immunogenic carrier proteins to maintain a contraceptive level of immunity.

Antigen Delivery Systems for a Fox Immunocontraceptive Vaccine

At present, three different vaccine delivery systems are being assessed to determine which will be the most effective for inclusion into the bait: (1) recombinant derived gamete antigen(s) encapsulated within microspheres, (2) a recombinant vaccinia virus capable of expressing foreign antigen(s) in the infected host, and (3) selected recombinant bacterial vectors such as the attenuated aroA strains of *Salmonella typhimurium.*

Microencapsulated Antigens

The effective oral presentation of antigens to the lower gastrointestinal tract is hampered by the degradation of protein within the stomach. A convenient way to overcome this is to use biodegradable microspheres that contain the entrapped antigen. These could be ultimately packaged within a bait, providing an effective oral delivery system whereby the vaccine antigen is delivered directly to the gut. The microspheres are taken up by the mucosae with the subsequent induction of a mucosal immune response (McGhee et al. 1992). In recent years, a number of investigators have reported the successful application of this technique for the delivery of antigens and the subsequent generation of mucosal immunity to the encapsulated antigens (Mestecky and Eldridge 1991).

We have recently completed a study to evaluate the efficacy of microspheres containing a recombinant sperm antigen to stimulate a mucosal immune response in rats (Muir et al. 1994). Microspheres were synthesized using the poly-DL-lactide-co-glycolide copolymer incorporating a recombinant source of the fox sperm protein FSA-1r (Bradley 1994). The oral administration of FSA-1r-loaded microspheres to rats resulted in a significant production of cells within the jejunum that were secreting IgA antibodies specific for the FSA-1r antigen. The level of stimulation was comparable to that obtained by either direct immunization of the Peyers' patches with microspheres containing antigen or unencapsulated antigen. These preliminary results indicate that further experiments would be worth pursuing to assess the utility of this approach for antigen delivery to foxes.

Viral Vectors

The use of recombinant vaccinia viral vectors containing the genes encoding selected sperm antigens may offer an excellent delivery system for an immunocontraceptive vaccine. For example, effective vaccination of foxes with a recombinant vaccinia expressing the rabies glycoprotein gene has proved enormously effective for immunizing foxes against rabies (Brochier et al. 1990). Building on these experiences, we are developing vaccinia vectors for application in immunocontraception. Such a system would allow further studies on the enhancement of the mucosal immunity, possibly by constructing vectors that coexpress IgA-specific stimulating cytokines (Ramsay et al. 1994).

A preliminary assessment of the immunological responses in foxes to the oral administration of a recombinant vaccinia viral vector expressing the hemagglutinin antigen (HA) has begun, and the results of these experiments will provide a basis for further experiments designed to test the utility of using a recombinant poxviruses for the delivery of immunocontraceptive antigens.

Bacterial Vectors

Recombinant bacterial vectors are an alternative delivery vehicle for a variety of vaccine antigens (Schodel 1992). The use of attenuated strains of *Salmonella typhimurium* as a live vector would be particularly applicable for stimulating reproductive tract mucosal immunity because *Salmonella* sp. colonize the intestinal tract and proliferate in the gut associated lymphoid tissue (Curtiss et al. 1989).

The use of selected mutant strains of *Salmonella* sp. has the advantage that they can be made avirulent without decreasing immunogenicity and are not infective outside the host. These considerations are important for any recombinant vaccine being considered for environmental release. However, a potential drawback is that immunity toward the carrier organism could develop, making subsequent exposure to the vaccine ineffective.

We have conducted an experiment to assess whether the attenuated *Salmonella typhimurium* aroA mutant strain is capable of stimulating mucosal immune responses in foxes after oral administration. Such information is a prerequisite to any future use of this organism as a vaccine vector. We have found that foxes given oral doses of *Salmonella typhimurium* readily produce serum immunoglobulin M (IgM) and IgG, and vaginal IgG and IgA antibodies to *Salmonella typhimurium* lipopolysaccharide over a 6-week period. The results indicate that foxes can respond immunologically to a single oral dose of *Salmonella*

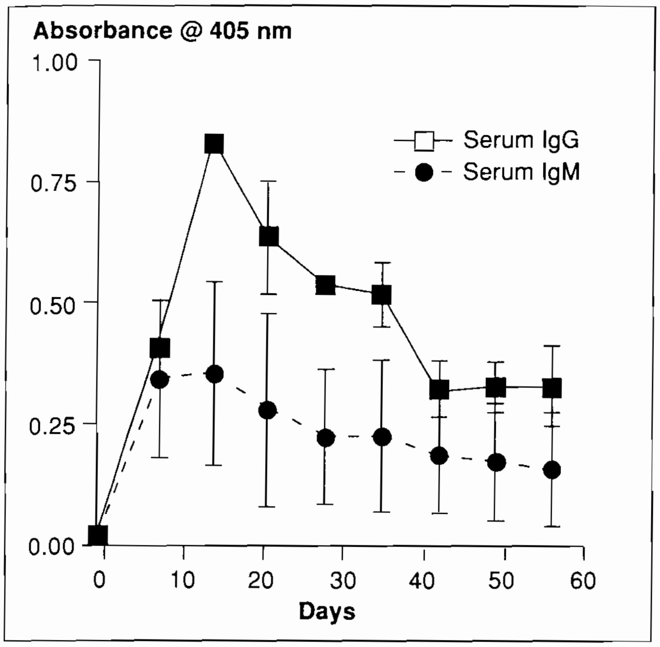

Figure 3. Serum IgG and IgM antibody responses (Mean ± SD; $N = 2$) in female foxes to lipopolysaccharide antigen after one oral dose of 5×10^9 *Salmonella typhimurium* (aroA mutant strain SL3261).

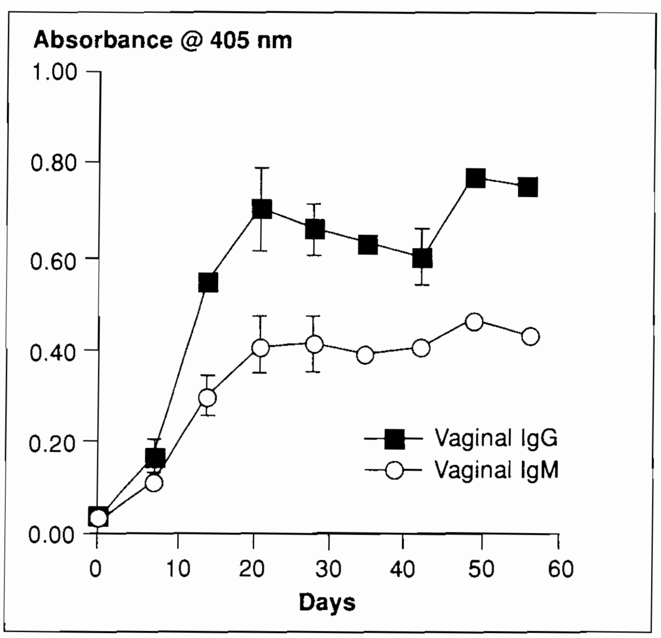

Figure 4. Vaginal IgG and IgA antibody responses (Mean ± SD; $N = 3$) in female foxes to lipopolysaccharide antigen after one oral dose of 5×10^9 *Salmonella typhimurium* (aroA mutant strain SL3261).

typhimurium that is sufficient to produce a high and sustained level of immunity within the female reproductive tract, albeit to a highly immunogenic antigen (figs. 3 and 4). Experiments are now in progress to construct a recombinant *Salmonella typhimurium* capable of expressing selected sperm antigens. Such recombinants will be screened for their ability to induce specific reproductive tract immune responses to the foreign antigen.

Concluding Remarks

Fertility control holds exciting prospects for the future management of wildlife populations. Internationally, a growing number of scientists and wildlife managers regard this approach as the only acceptable future method of managing wildlife populations. However, the obstacles that will be encountered in the development and implementation of such a technology are substantial. If the effort is successful, the rewards will be substantial, too. Each species will yield its own set of unique challenges.

In this overview, I have summarized key aspects relating to the reproductive and immunological studies that are required in the process of developing an immunocontraceptive vaccine for a vertebrate pest species. I have attempted to address, albeit in a rather brief way, the major considerations that need to be taken in to account when contemplating the development of a fertility control vaccine for wildlife. I have not considered the wider ecological implications of fertility control being imposed on a wildlife population. Such studies pose a whole new set of questions and challenges, and any project concerned with fertility control of wildlife will require a large, integral ecology research program to match the other facets of the work. Eventually, it will be the ecological studies that will assess both the impact and long-term consequences of fertility control on a particular wildlife population.

Acknowledgments

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Potential Use of Contraception for Managing Wildlife Pests in Australia

By Mary Bomford and Peter O'Brien

Abstract: There is an increasing level of interest in contraception to manage wildlife pests in Australia, due mainly to concerns over high recurrent costs, animal welfare, and the failure of current control techniques to prevent damage in some instances. We have developed criteria that need to be met for contraception to be successful for pest control:

- Technology exists to reduce fertility.
- An effective delivery mechanism to treat wild animals exists.
- The end result of reduced animal damage is achieved.
- Effects are humane and nontoxic.
- Product is target specific, cost effective, and environmentally acceptable.

We assessed all available and proposed contraceptive techniques against these criteria to see if any were suitable or promising for use on Australian pests. The present role of contraception in Australia is extremely limited. The main barrier for widespread and abundant pests is the lack of suitable delivery techniques that are cost effective. The probable impact of contraception on wild populations is also poorly understood. High rates of infertility may be necessary to control pest populations and the damage they cause. Even if the fertility of wild pest populations can be reduced, there is no guarantee that this will be as effective as lethal techniques for reducing pest numbers. The longer term potential of contraception in managing wildlife damage will depend on the outcome of future research and development, particularly in the fields of contraceptive delivery and the effects of fertility control on population dynamics.

Introduction

The Australian government is interested in contraception to manage wildlife pests because of concerns over high recurrent costs of lethal controls, and their failure to prevent damage in some instances (Senate Select Committee on Animal Welfare 1991, Wilson et al. 1992). Also, many people are concerned about animal welfare issues associated with lethal techniques used to control vertebrate pests in Australia, particularly the shooting of kangaroos and feral horses. Wildlife contraception is often perceived as a more humane alternative. As a constructive response to this concern, we evaluated the scientific literature on the use of fertility control for wildlife management to assess the potential value of fertility control for wildlife management in Australia (Bomford 1990 and 1990 unpubl., Bomford and O'Brien 1990 unpubl. and 1992). This paper, which summarizes and updates the findings of these studies,

- describes the impacts of pest animals,
- identifies the objectives of wildlife contraception,
- identifies criteria for its successful use,
- evaluates its potential application in Australia, and
- identifies promising research directions.

Impacts of Pest Animals

Australia's main introduced vertebrates that have established wild pest populations are European rabbits *(Oryctolagus cuniculus),* European red foxes *(Vulpes vulpes),* horses *(Equus caballus),* cats *(Felis catus),* dogs and dingoes *(Canis familiaris),* goats *(Capra hircus),* pigs *(Sus scrofa),* buffalo *(Bubalus bubalis),* donkeys *(Equus asinus,)* house mice *(Mus domesticus),* and European starlings *(Sturnus vulgaris).* All these species are widespread and abundant, and many are perceived to cause losses to conservation values and agricultural production over much of their range, which makes their control expensive (Wilson et al. 1992).

Rabbits, Australia's most significant vertebrate pest, have been estimated to cost $50 million (U.S.) a year in lost agricultural production (Flavel 1988). This figure does not include the damage rabbits inflict by competing with our native animals and destroying their habitat, preventing tree regeneration, and contributing to soil erosion (Williams et al. 1995).

Foxes are major predators of wildlife (Kinnear et al. 1988, Saunders et al. 1995). Their distribution corresponds to areas where there have been many extinctions of small and medium-sized native mammals and where many more species are endangered (Wilson et al. 1992). Foxes also prey on lambs (Saunders et al. 1995), and there is a small risk that foxes could become a rabies vector should this disease be introduced to Australia (Forman 1993).

Feral horses are believed to compete with native species and livestock for pasture and water and cause soil erosion (Dobbie et al. 1993). There are estimated to be more than 300,000 feral horses in Australia, about four times the number in the United States (McKnight 1976, Clemente et al. 1990). They often inhabit remote regions, where they build up to high numbers during good years, and many starve during drought (Wilson et al. 1992).

Some native species are also a problem. For example, native parrots damage cereal and fruit crops (Bomford 1992). The large red and grey kangaroos *(Macropus rufus, M. giganteus,* and *M. fuliginosus)* have increased in range and abundance since European settlement due to the provision of livestock watering sites and extension of grasslands (Robertson et al. 1987). They compete with livestock for pasture and also reach extremely high densities in some national parks, sometimes threatening the survival of native plant communities in these reserves (Caughley 1987, Shepherd and Caughley 1987).

Wildlife managers currently control pests by poisoning, shooting, and habitat manipulation, with trapping, biological control, and exclusion being used to a lesser extent (Wilson et al. 1992). These are currently the only cost-effective means known for wildlife damage control.

Objectives of Fertility Control

The objective of fertility control for wildlife management may be one or more of the following:

- Reduce control costs,
- Achieve more humane control,
- Minimize impact on nontarget species,
- Reduce population growth, and/or
- Reduce animal damage.

When native species are a pest, the control technique used to reduce damage must not put the survival of the species at risk.

Criteria for Successful Use

We believe the following set of seven criteria need to be met for successful wildlife contraception. We examine currently available and proposed fertility control techniques to see how well they meet these criteria.

Criterion 1: Available Drug or Technique To Reduce Fertility

Many chemicals and techniques are known to cause infertility in captive animals (Kirkpatrick and Turner 1985, Marsh 1988, Kirkpatrick et al. 1990 and 1992, Bomford 1990). Much of this knowledge has been acquired from the huge investment in human contraceptive research. The use of contraception for wildlife management is not restricted by a lack of suitable techniques or drugs. So the availability of suitable agents for causing infertility in wildlife is unlikely to be a barrier for pest management.

Criterion 2: Effective Delivery Mechanism To Treat Wild Animals

The lack of practical techniques to deliver drugs to wild populations is a major obstacle to using contraception for controlling wildlife pests. Many tests on captive animals have relied on drugs delivered by surgical implantation, injections, biobullets, or by frequent oral dosing (Noden et al. 1974, Marsh 1988, Plotka and Seal 1989, Plotka et al. 1992). Such delivery techniques are either technically impossible or prohibitively expensive for reducing the damage caused by widespread and abundant wildlife, such as the estimated 200 million to 300 million wild rabbits that cause damage over much of Australia's rangelands (Flavel 1988, Wilson et al. 1992, O'Neill 1994, Williams et al. 1995). No remotely deliverable contraceptive agents cause infertility for more than 1 year, so delivery has to be repeated at least on an annual basis. Many orally active synthetic drugs require frequent ingestion, or delivery has to be precisely timed in relation to the breeding cycle, which may vary with environmental conditions. The suitable period may be as short as 2 weeks for some birds (Lacombe et al. 1986). It is extremely doubtful that these limitations to chemical fertility control could be overcome for effective pest management in Australia.

Development of a single-dose, long-acting or permanent contraceptive would reduce the difficulty and cost of delivery using the techniques described above (Marsh 1988, Berman and Dobbie 1990 unpubl.). The use of a live disseminating-recombinant virus for delivery, which is species specific to the target pest, could further reduce the technical difficulty and expense for some pests (Tyndale–Biscoe 1991 and 1994). But this technology is still under development and even if it is successful, it is unlikely to be available for another decade.

Criterion 3: End Result Is Reduced Animal Damage.

The focus of research on wildlife contraception has been on reducing fertility of pest animals. Doing that is not enough. The goal must be to reduce pest numbers and so reduce damage caused by the pest (Braysher 1993). We found no field studies that demonstrated such effects. Without field studies to examine, we turned to population theory to see what could be expected.

Australia has a highly variable rainfall. Many pest animals build up to high numbers in good seasons when food is abundant and then have their most severe impacts during droughts (Morton 1990, Dobbie et al. 1993, Williams et al. 1995). At these times, they compete with stock and native species for food and water, prey on native species in refuge habitats, and overgraze the land, causing erosion and killing tree seedlings. Many pests, such as feral horses, kangaroos, and rabbits, naturally stop breeding during droughts (Shepherd 1987, Wilson et al. 1992, Williams et al. 1995), so fertility control is not a useful population control tool at such times.

The theoretical effects of killing or sterilizing animals were compared to assess the potential value of contraception as an alternative to lethal controls (Bomford 1990, Bomford and O'Brien 1990 unpubl.). Expanding populations which were unlimited by resources were examined first (fig. 1). In such populations, it is usual for most healthy adults to breed, for juvenile survival to be high, and for the population to have exponential growth.

If half the adult population is killed (fig. 1A), exponential growth resumes, and the population soon recovers to its original density. If half the adult population is sterilized (fig. 1B), using a technique that causes loss of fertility without altering behavior,

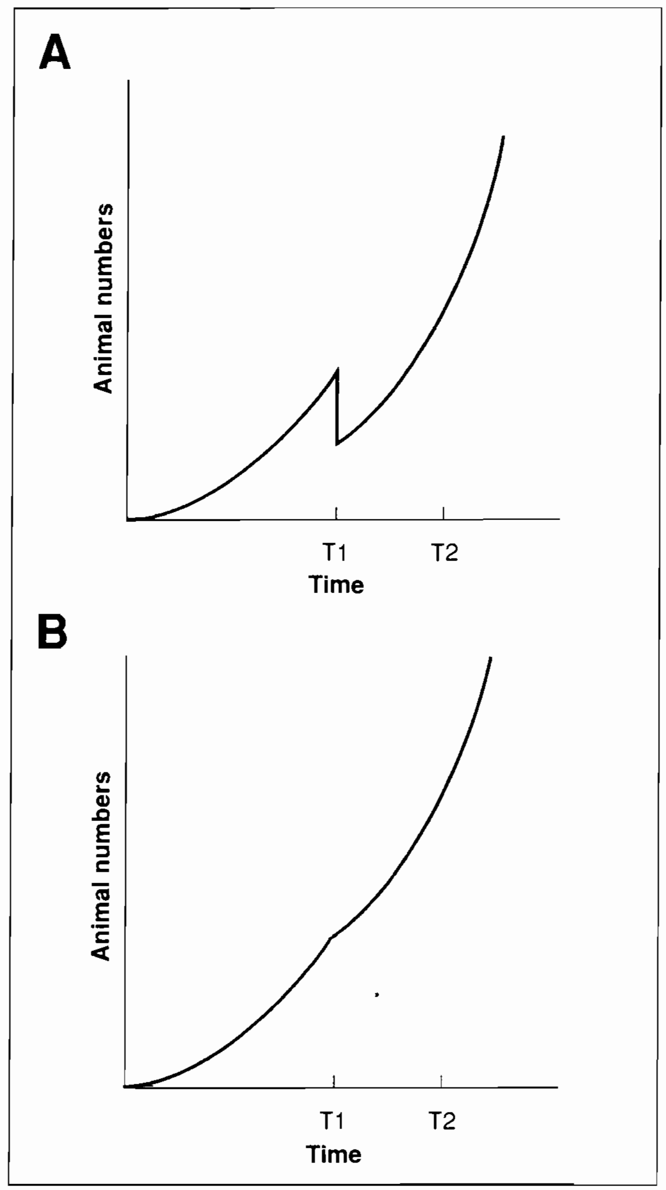

Figure 1. Exponential density-independent population growth. (A) Half population killed at time T1. (B) Half population sterilized at time T1. Killing is more effective for reducing population size.

population growth continues but at a slower rate than would have occurred in the absence of sterilization. Hence, for growing populations, killing or culling is more effective for reducing population growth rates than sterilizing an equivalent number of individuals. This conclusion was also reached by Garrott (1991) through mathematical modeling of the response of feral horse herds to changes in survival or fecundity.

If repeat treatments are used to kill or sterilize new animals over time, as opposed to the single treatment illustrated in figure 1, or if a higher proportion of animals is treated, population growth rates will flatten for both killing and sterilizing treatments, especially at low densities. But the same principle applies, and killing acts to double advantage: not only are dead animals removed from the population, they also do not breed. So by simple arithmetic, it is clear that killing will reduce the population more than contraception if the same number of animals are treated.

We concluded from this that sterilization is likely to be most effective to slow the rate of recovery of a population after some other factor, such as poisoning, shooting, drought, or disease, has reduced numbers to low levels. Hone (1992) also reached this conclusion from his mathematical modeling of population responses to contraception. Killing equal numbers of animals will be more effective than contraception for growing populations, irrespective of the proportion of the population treated.

Stable populations with density-dependent regulation at environmental carrying capacity, limited by available resources, such as space, food, or nest sites, were also examined (fig. 2). In such populations, dominance or territorial behavior often prevents some healthy adults from breeding or causes them to breed in suboptimal habitat or under social conditions where success is low. Juvenile survival is usually poor.

If half the adult population is killed (fig. 2A), logistic growth occurs and the population recovers rapidly. If half the adult population is sterilized (fig. 2B), several different responses in the population are possible, depending on the nature of the density-

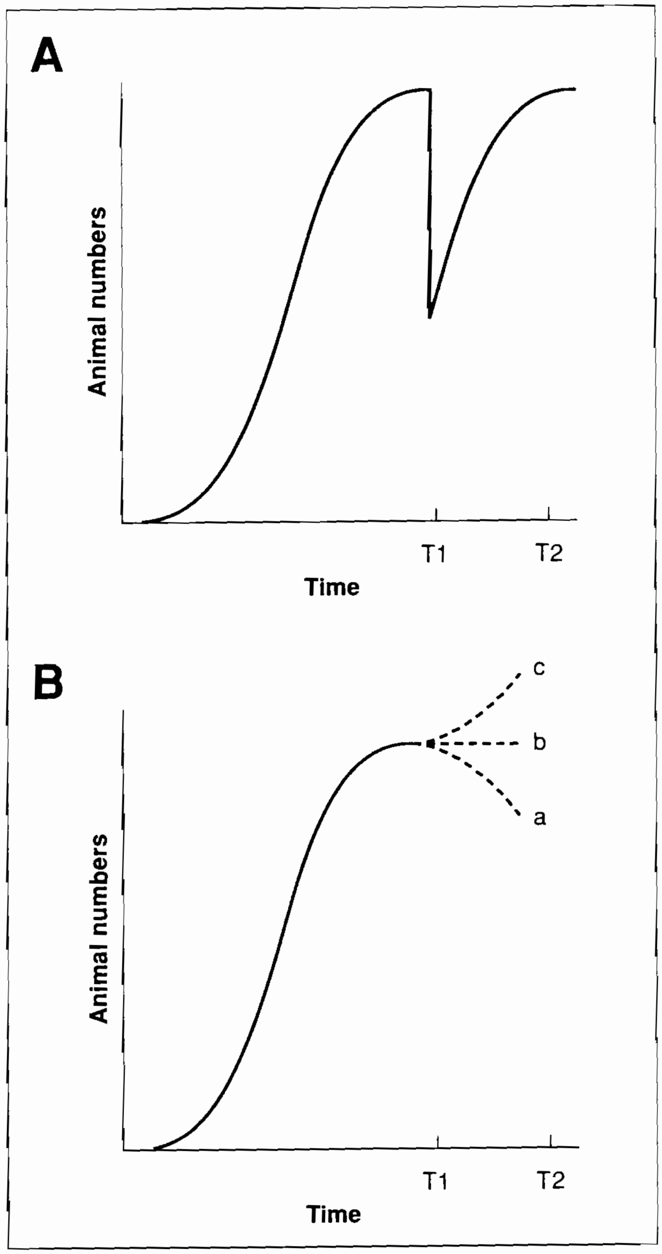

Figure 2. Logistic density-dependent population growth. (A) Half population killed at time T1. (B) Half population sterilized at time T1. In the short term, killing is more effective for reducing population size. In the longer term, the relative advantages of killing or sterilizing depend on the population response to the contraceptive treatment (B—lines a, b, and c), particularly in relation to the duration of sterilization, behavioral changes in treated animals, and compensatory changes in reproductive success of untreated animals and in survival.

dependent regulation and the response of the population to the treatment. A decline in population density (fig. 2B.a) is the response most people expect. Such declines may well occur in certain circumstances, but in some instances contraception may not cause a decline (fig. 2B.b), or it may even destabilize social behavior and lead to a population increase (fig. 2B.c).

Compensatory responses can prevent population declines, even if the contraceptive treatment does not interfere with sexual or social behavior. Compensatory responses may include increased survival, increased birth rates in untreated fertile individuals, increased immigration, and reduced dispersal. For example, many populations have high juvenile mortality. Sterilization may simply prevent the birth of young that would otherwise die or disperse without breeding. Even quite high reductions in fertility will not reduce population density if birth rates are still sufficiently high to allow normal numbers of young animals to join the adult population.

The extent of compensation determines whether fertility control will work and how well it will work. Unfortunately, we know little about the extent to which compensatory factors operate in pest populations following contraceptive treatment. We found many of the published models on the effects of contraception on population dynamics took inadequate account of such compensatory factors (Sturtevant 1970, Knipling and McGuire 1972, Spurr 1981, Bomford 1990, Bomford and O'Brien 1990 unpubl.).

Compensatory responses, such as increased breeding, survival, or immigration, can also be expected following population control by killing and can lead to rapid recovery of culled populations. Annual rates of increase in culled populations have been estimated at 20 percent for feral horses (Eberhardt et al. 1982), 23 percent for feral donkeys (Choquenot 1990), and 75 percent for feral goats (R. Henzell, pers. comm.). We could find no research that compared the extent of compensatory responses following killing or contraception in wildlife populations. Stenseth (1981), however, modeled pest control processes, including parameters for natality, mortality, dispersal, and immigration rates, all of which allowed for the effects of compensation. He found the higher the age-specific mortality rate (population turnover rate) of an uncontrolled population, the more likely it is that reduction in reproduction will be the optimal pest control strategy (as opposed to increased mortality or decreased immigration). If the equilibrium density of the population is low, the optimal pest control strategy will most often be to increase mortality rates as much as possible, especially if the mortality rate is naturally low. If, however, a pest species is long lived, and a contraceptive that lasts several years following a single treatment is used, the proportion of sterile individuals in the population may increase with successive treatments. In such circumstances, sterilizing animals may be more effective for reducing population growth rates than killing equal numbers.

When drugs used to sterilize animals cause a change in social behavior and territorial behavior or dominance is lost, a population could increase. This has been demonstrated in a model published by Caughley et al. (1992) showing that random contraception of a proportion of the females in a population could lead to increased production of young if the contraceptive treatment overrode suppression of breeding exerted by dominant females over subordinate females within social groups. The occurrence of this response would depend on social group and litter sizes, and in most circumstances the model of Caughley et al. (1992) indicated that contraception would reduce breeding.

A field study conducted on sheep on Soay Island showed that if contraception alters social behavior it may be counterproductive in terms of damage control (Jewel 1986). Male lambs were castrated in feral sheep flocks which had density-dependent regulation of numbers through food supply. After 4 years, 61 percent of castrated males had survived, in contrast to only 6 percent of untreated males. Sterilized males also spent more than twice as much time feeding as fertile males. Hence, in this study, sterilizing part of the population increased survival and may have increased food consumption. This important finding illustrates the need for contraceptive approaches that do not cause undesirable changes to endocrine function and behavior.

If damage mitigation rather than lower reproductive success is the objective, fertility control may not be an advantage. It may even be counterproductive, if it allows large numbers of nonbreeding individuals to remain in a population. So we concluded that scientists need to greatly improve understanding of the factors regulating populations of pest species and how these are affected by fertility control. Without precise information on these relationships, scientists cannot predict whether contraception will be an effective tool for controlling wildlife damage. More sophisticated models, based on good field data, are needed. In particular, investigators need a better understanding of the proportion of animals in pest populations that need to be rendered infertile to bring densities down to levels where damage is controlled.

Criterion 4: Humane and Nontoxic Effects

Fertility control drugs can affect animal health. Some have unpleasant side effects, and some are toxic or carcinogenic (Lofts et al. 1968, Cummins and Wodzicki 1980, Johnson and Tait 1983). But in general, this is an area where fertility control performs well relative to lethal control techniques.

Criterion 5: Target Specificity

Unfortunately, few fertility-control drugs are species specific, so nontarget wildlife, domestic species, or people could be affected. This is, of course, also true for many lethal control techniques (McIlroy 1986). The doses of chemosterilants necessary to cause infertility in target pests may be toxic or lethal for other species (Ericsson 1982, Johnson and Tait 1983, Saini and Parshad 1988). Immunological fertility-control agents spread by genetically engineered organisms could be made target specific for some species. But this may be a problem for feral pests with domestic counterparts, or those closely related to protected native species. There is also a risk that modified viruses could mutate to infect species other than their original hosts (Tiedje et al. 1989). But mutation would not cause the new hosts to become infertile if the virus were engineered to affect genes or proteins present in the target species only.

Criterion 6: Environmental Acceptability

In contrast to many vertebrate poisons, most fertility-control drugs do not leave residues that are harmful to the environment, though some chemosterilants could be unsuitable for use in food crops (Marsh and Howard 1973).

Criterion 7: Cost Effectiveness

Pest-control benefits must exceed costs. Preferably, the technique chosen and level of application should maximize the benefit–cost ratio. In calculating the relative costs and benefits of alternative techniques, assessments of the value of moral and animal welfare issues need to be considered. Some benefits may be difficult to quantify, such as the benefits of protecting endangered native species. Cost effective damage control occurs when the cost of pest control is more than met by savings in protecting all values society wants (Braysher 1993).

Cost is a major obstacle in the employment of fertility control as a wildlife management technique using current technology. Although the technology for fertility control of individuals does exist, contraceptive chemicals and their delivery can be prohibitively expensive for widespread and abundant pests (Matschke 1980, Berman and Dobbie 1990 unpubl.). Most of the more expensive techniques for fertility control, such as those requiring surgery, implants, or frequent or continuous dosing over extended periods, are likely to be cost effective for only small numbers of valuable animals, such as those in exhibition parks or small private collections. In contrast, lethal control techniques are often cost effective for pests such as rabbits, feral horses, and foxes (Dobbie et al. 1993, Bomford and O'Brien 1995, Williams et al. 1995).

Application to Australian Pests

Control on a National Scale

For widespread and abundant pests, such as rabbits, rodents, foxes, and feral cats, horses, and pigs, no currently available contraceptive technique can provide cost-effective damage control. Only research into contraceptives disseminated passively by live organisms has promise for wide-scale control of such pests in the future. Research is currently being conducted in Australia on viral-vectored immunocontraception for the control of rabbits and is planned for wild house mice. Viral-vectored immunocontraception has the potential to bring great benefits to wildlife pest management in Australia and its development is a current research priority. There are, however, many technical hurdles to be overcome, and it is too early to predict whether the research will be successful. In addition, there are social considerations that may impede the development and use of viral-vectored immunocontraceptives. For example, there is a risk that a live immunocontraceptive virus for rabbits could be accidentally transported to other countries where lagomorphs are not pests. It is also probable that some sections of the community would oppose the release of an immunocontraceptive virus due to perceptions of risk to nontarget species.

Control on a Local Scale

Contraception could also be used in Australia for localized control of relatively small numbers of pest animals. Contraceptives delivered through baits, implants, or injections might be used to reduce the damage caused by small numbers of pest animals such as kangaroos, feral horses, or foxes in a localized area. An example might be to use contraceptives to reduce pest numbers to protect endangered flora or fauna in a reserve. The technology is certainly achievable. Delivery would be a major expense, but in an intensively managed area, where shooting or other lethal controls are unacceptable for public-safety or public-relations reasons, or due to the risks to nontarget species, the high cost of delivery using baits or remotely delivered injections might be acceptable. Contraceptives are most likely to be suitable for species with short breeding seasons, where drug delivery is necessary for only a few weeks each year. For species with longer breeding seasons, a contraceptive would need to be developed for which a single dose lasts for at least 3 years to reduce delivery costs.

Research is currently being conducted to develop an immunocontraceptive for fox control. Despite an extensive search, no suitable live vector has been found for its delivery. But if a fox immunocontraceptive is successfully developed, it may be possible to use a bait delivery system for fox control in localized areas.

Conclusion

Currently available contraceptive techniques cannot be used to control Australia's widespread and abundant pest animal species. There are two main problems for using contraception for wide-scale control of any of our major pests. First, there are no suitable techniques for cost-effective delivery, which will be prohibitively expensive for broad use unless passive delivery via a live agent becomes available. Second, researchers lack knowledge about the factors regulating pest populations and the potential effect of fertility control on pest population dynamics. Field experiments are needed to determine if immunocontraceptives can reduce pest populations to the extent needed to control damage. Australian research is focused in these priority areas, but there are many technical hurdles, and success, if it comes, will not be for some years.

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Henzell, R. Animal and Plant Control Commission, GPO Box 1671, Adelaide SA 5001, Australia.

Research To Develop Contraceptive Control of Brushtail Possums in New Zealand

Simon E. Jolly, Phil E. Cowan, and Janine A. Duckworth

Abstract: Common brushtail possums are serious pests in New Zealand, where they threaten the survival of native plants and animals and spread bovine tuberculosis. A National Science Strategy Committee established in 1991 to coordinate possum research gave high priority to research aimed at biological control of possums, particularly contraceptive control. Surveys are identifying pathogens and potential vectors, and research has begun on immunology, gene transcription, potential contraceptive targets, and sociobiology. As there are more than 60 million possums in New Zealand, contraceptive vaccine delivery systems need to be cost effective, and they must be publicly acceptable. A vaccine could be included in a bait, but long-term cost-effective control will probably require a biological vector. Eventually the best control strategy will probably combine traditional control and immunocontraception.

Keywords: brushtail possums, immunocontraception, *Trichosurus vulpecula,* vectors

The Possum Problem

The common brushtail possum *(Trichosurus vulpecula),* a native Australian marsupial, was introduced into New Zealand in the last century to start a fur industry. Possums are folivorous and largely arboreal, and they average about 3 kg in weight. They are relatively widespread in Australia, although not often in high number. Like all marsupials, they are legally protected in Australia (How 1983). In contrast, possum population densities are 5 to 20 times higher (up to 25/ha [Green 1984]) in New Zealand, where the possum is acknowledged as the most serious vertebrate pest (Parliamentary Commissioner for the Environment 1994).

Possums established themselves so successfully in New Zealand partly because the forests evolved in the absence of any mammalian browser. Lacking specific chemical defenses against such an attack, many native trees and shrubs are highly palatable to introduced herbivores. There are also no significant possum predators in New Zealand. The large possum population is degrading the composition and structure of some forest types (Payton 1987, Stewart and Rose 1988, Allen et al. 1989). Populations of native animals are also affected because possums compete with them for fruit and nectar supplies (Cowan 1991). Predation, disturbance, and competition are reducing the survival and reproductive success of endemic and highly endangered species such as the kokako *(Callaeas cinerea)* and the short-tailed bat *(Mystacina tuberculata)* (Leathwick et al. 1983, Brown et al. 1993).

In addition to such impacts on conservation values, possums are the major wildlife host of bovine tuberculosis (Tb) in New Zealand. Possums maintain this disease and spread it to cattle and deer herds (Livingstone 1986, 1991), threatening the country's livestock exports. In the 1993–94 financial year, NZ$17 million was spent on Tb eradication programs in cattle and deer herds and NZ$18 million was spent on possum control in Tb endemic areas (Parliamentary Commissioner for the Environment 1994). Possum control is chiefly dependent on the use of Compound 1080 (sodium monofluoroacetate) baits, but public opposition to the widespread use of this poison is increasing with particular concern about possible environmental contamination.

In October 1991, the New Zealand Government recognized the seriousness of the possum threat to the economy and environment by establishing a National Science Strategy Committee (NSSC) to coordinate possum research. The NSSC has given a high priority to research on the biological control of possums, with contraceptive control as a major focus (Atkinson and Wright 1993). Biological control options for possums were discussed at a workshop hosted by the NSSC for New Zealand and Australian scientists in October 1992. There was general consensus that too little was known about some fundamental aspects of possum biology to embark on a focused project like that for rabbit and fox control in Australia (see Tyndale–Biscoe, this volume). It was agreed that basic research was required in seven priority areas (table 1). This chapter describes some of the research that has been initiated and the philosophy underlying the research priorities.

Table 1. Priority research areas (not in order) for the biological control of common brushtail possums in New Zealand

1	*Screening for pathogens and potential vectors*	The National Science Strategy Committee is open to the possibility of identifying organisms that could be used for classical biological control as well as organisms that could be used to vector contraceptive vaccines.
2	*Immunology*	These are both vital for the development of contraceptive vaccines.
3	*Gene transcription*	
4	*Control of reproduction through the central endocrine system*	Studies in these fields aim to identify potential contraceptive vaccine targets.
5	*Biology of sperm, eggs, and the reproductive tract*	
6	*Control of lactation*	
7	*Sociobiology*	This is an important area of research in regard to the transmission of vectors and the behavioral consequences of contraceptive vaccines.

Research Priorities

Pathogens and Potential Vectors

Possum parasites and pathogens are being comprehensively surveyed in New Zealand and Australia to identify organisms for use as classical biological control agents or as vectors of contraceptive vaccines (Heath et al. 1994). Because New Zealand's possum population was founded from only a few hundred animals and some intermediate hosts are not present in New Zealand, possums in this country probably carry fewer types of parasites and pathogens than those in Australia (Cowan 1990). Also, because New Zealand's possum population has been isolated for more than 100 years, it may be more susceptible than the Australian population to the broader range of parasites and pathogens present in Australia.

In New Zealand, approximately 200 possums were trapped in 1993 and 1994 in each of eight locations close to the original possum release sites. These animals have been examined for the presence of ectoparasites and endoparasites, and samples from the heart, lung, liver, spleen, and gut have been screened for bacteria and viruses. Comparative studies will begin in Australia shortly.

Immunology

The New Zealand Pastoral and Agricultural Research Institute (AgResearch) is working on the immune response of possums. This research is primarily focused on the kinetics of antibody production in the possum against particulate and soluble proteins, and on determining optimal systems for stimulating high antibody responses at both the parenteral and secretory level. Early results indicate that cell-mediated responses are generally poor in the possum, which relies more on antibody responses. Responses to particulate antigens (e.g., whole sperm) are considerably stronger than responses to small soluble antigens (B. Buddle, pers. comm.). The cytokines that regulate immune responses in possums are being identified.

Gene Transcription

Although gene transcription is one of the research priorities, there appears to be little current research. AgResearch has started investigating how foreign DNA is expressed in nematodes and considering how nematodes might be used as vectors of contraceptive vaccines. A number of groups are preparing c-DNA libraries, including those for the pituitary (AgResearch, Wellington), the mammary gland (University of Otago, Dunedin), and the testis and female reproductive tract (Marsupial Cooperative Research Centre, Macquarie University, and La Trobe University, Australia).

Potential Contraceptive Targets

Central Endocrine System—Gonadotropin-releasing hormone (GnRH) is central to the regulation of reproduction and has therefore been suggested as one possible target of a contraceptive vaccine. Vaccines against GnRH are easily produced. Because the hormone is present in the body in tiny amounts, antibodies produced by GnRH vaccines can readily remove the hormone from circulation.

A major disadvantage is that the structure of this hormone is identical in all mammals and birds, so GnRH vaccines would not be possum specific. It is possible, however, that species-specific regions may be present on GnRH receptors or that gene regulators may have species-specific regions. AgResearch in Wellington is investigating the regulation of GnRH gene expression.

Another disadvantage of GnRH vaccines is that they effectively neuter animals so that social behaviors that are dependent on sex steroids are likely to change in vaccinated animals. At Landcare Research, Christchurch, investigators are testing the behavioral effects on possums of a commercial GnRH vaccine registered for use in cattle in Australia (Hoskinson et al. 1990). Captive groups of one male and two female possums are observed regularly after the dominant female has been vaccinated with the GnRH vaccine. This work is still at an early stage, but the vaccine does not seem to affect the social status of the dominant possums.

Biology of Sperm, Eggs and the Reproductive Tract—At Landcare Research, we are focusing on sperm, eggs, and the fertilization process. We are investigating the immunological responses of possums to sperm vaccines and collaborating with Macquarie University, Australia, to characterize specific antigens of possum sperm and zona pellucida. Targeting gametes has advantages because many antigens are potentially possum specific, and an immunological attack on sperm or eggs should not affect behavior. Sperm vaccines are attractive. If sperm are attacked in the female tract before fertilization, this will disrupt fertility in females as well as in males. Repeated insemination of infertile females may also act as a booster vaccination and result in a long-lived immunity.

Vaccines have been prepared from whole sperm using Freund's Complete and Freund's Incomplete adjuvants. We are studying the effect of the vaccine on fertility and the relationship between fertility and antibody titre. The Macquarie group is also working on in vitro fertilization (IVF) systems for possums using Tammar wallabies *(Macropus eugenii)* as a marsupial model (Mate and Rodger 1993). An IVF system will greatly facilitate the characterization of gamete antigens and ultimately be essential for screening potential vaccine antigens. Because possums are marsupials, we hope that the gamete antigens are different from those of eutherian mammals. However, there appears to be some homology between possum and eutherian zona pellucida proteins (J. Rodger, pers. comm.); detailed characterizations are yet to be done on the sperm surface proteins of the possum.

Secretions of the female reproductive tract are important for the transport of sperm, eggs, and early embryos, as well as being vital for growth and survival of the conceptus. The Macquarie University group plans to characterize some of the secretory proteins as an immunological attack directed at some of these may result in infertility. Workers at AgResearch in Dunedin are identifying functional aspects of the female reproductive tract that may be susceptible to disruption by estrogenic plant compounds. This group is considering the possibility of being able to genetically modify food plants favored by the possum so that they deliver contraceptive compounds (B. McLeod, pers. comm.). Initial work concentrates on normal function of the reproductive tract, looking at the cyclical changes in the ultrastructure of the tract, secretory organelles, and mucoid secretions.

Control of Lactation—Disruption of lactation is not true contraception, but is an option with possums, which, like all marsupials, invest in lactation rather than pregnancy. Pregnancy in possums lasts only 17 days; lactation lasts up to 230 days (Pilton and Sharman 1962). An immunological attack could suppress milk production or change the composition of the milk so that it does not provide the appropriate nutrients. In possums and some other marsupials, cessation of lactation is a natural method of population regulation: when conditions in the wild are unfavorable, lactation ceases and pouch young die. In some years, up to 50 percent of possum pouch young may die in this way. The pouch young has limited sensory development until it is nearly 3 months old (Lyne and Verhagen 1957, Hughes and Hall 1984), so targeting lactation in the early stages of development is considered relatively humane.

The composition of the milk undergoes marked changes during the long suckling period in marsupials (Tyndale–Biscoe and Renfree 1987). At Landcare Research, we are investigating changes in the elemental composition of possum milk during the course of lactation. Sodium, potassium, iron, and copper all show marked changes. We are especially interested in milk calcium levels. Brushtail possums develop metastatic calcinosis when fed a diet high in calcium, and calcium metabolism is readily disrupted in possums by cholecalciferol (Eason 1991). Also in progress is work to model the effects of lactation disruption on pouch young using the prolactin inhibitor bromocriptine. The aim of this project is to quantify the relationship between milk production and growth and survival of the pouch young.

Otago University is characterizing possum milk proteins. Researchers at the university have identified some unusual proteins associated with certain stages of lactation that are analogous to late lactation protein in Tammar wallabies *(Macropus eugenii)* (Nicholas et al. 1987), but the significance of these to the developing pouch young has not yet been established (M. Grigor, pers. comm.).

Sociobiology

Behavioral changes caused by contraceptive vaccines could compromise their efficacy. Possum social organization is based around dominance hierarchies (Winter 1976, Biggins and Overstreet 1978). If sterilization affects social behavior, changes in social structure could allow subordinate individuals to increase their breeding success. Landcare Research has been studying whether sterilization will affect social status. Females are more aggressive than males (Winter 1976, Oldham 1986), and our trials have shown that in captivity females retain their dominance status even after ovariectomy. The status of males also appears unchanged by castration (P. McAllum, unpubl. data). We plan further work to untangle the behavioral effects of sex steroids from learned behaviors and to ascertain that the results of pen trials are applicable to free-living populations.

Future Directions

Vectoring a Vaccine

As there are more than 60 million possums in New Zealand (Cowan 1991), vaccine delivery must be cost effective. A vaccine included in a bait is the likely research target for the medium term (6 or 7 years). However, long-term, cost-effective control will probably need a self-sustaining biological vector such as a genetically modified virus (as proposed for rabbit and fox control in Australia; Tyndale–Biscoe, this volume), bacterium, or nematode. At this early stage, the New Zealand research program is keeping all options open.

Any vector would need to meet rigid specifications to allay the concerns of the public and New Zealand's trading partners. It would need to be humane and unable to survive away from possums, so that it could not cross to Australia, where possums are protected. The vector must infect only possums, and its mode of action must also be possum specific. The last two criteria act as a double safeguard.

Expectations

A biologically vectored vaccine is unlikely to eradicate possums because its success would be inherently dependent on the density of the possum population. When a population is dense, the level of possum to possum contact is high, and a vectored vaccine would have a significant impact. As a population declines and possums became more sparsely distributed, transmission of the vectored vaccine would be reduced. The population would equilibrate at a new lower level but not decline to extinction. This density-dependent effect could largely be circumvented by the use of a sexually transmitted vector. Possums actively seek partners in the breeding season, so a venereal infection is likely to persist even at low population levels.

A venereal vector would have other advantages. Any contraceptive vaccine would probably rely on the mucosal immune system to cause infertility, so sexual transmission of the vector delivers the vaccine to exactly where it can be most effective. The use of a sexually transmitted organism would also allay the concern that the vector might cross to Australia and infect protected possums there.

Computer modeling is currently defining the ecological and epidemiological criteria that need to be met to minimize the impact of possums. Modeling suggests that the possum population must be reduced to about 40 percent of its present level for 8–10 years to eradicate bovine tuberculosis (Barlow 1991). Such a reduction is theoretically achievable with a vectored contraceptive vaccine. Target reductions in possum numbers to protect conservation values are more difficult to quantify because of the diversity of the conservation values society wants to protect. This is an area of active research. The likely timetable for research and development of effective biotechnological control strategies for possums is in the order of 10 to 20 years, so New Zealand will have to depend on traditional pest control technologies for some time yet. Eventually the best control strategy will probably combine traditional control and immunocontraception (Barlow 1994).

In the coming years, new technologies will offer new possibilities for the control of vertebrate pests. The future promises some exciting research. We believe that it is only through the use of biotechnologies such as vectored immunocontraception that control of this pest can become truly sustainable.

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Buddle, Bryce. AgResearch, Private Bag, Upper Hutt, New Zealand.

Grigor, Murray. Department of Biochemistry, University of Otago, P.O. Box 56, Dunedin, New Zealand

McAllum, Priscilla. Entomology Department, Lincoln University, P.O. Box 84, Lincoln, New Zealand.

McLeod, Bernie. New Zealand Pastoral Agricultural Research Institute, Ltd., Private Bag 50034, Mosgiel, New Zealand

Rodger, John. Marsupial CRC, Macquarie University, New South Wales 2109, Australia.

Immunosterilization for Wild Rabbits: The Options

C. H. Tyndale–Biscoe

Abstract: Control of wildlife pest populations by sterilization could be more effective than conventional mortality agents, provided that two conditions are met: (1) the endocrine function of affected animals is not compromised, so as to exploit the natural suppression of reproduction of subordinate members of the population that occurs in many species; and (2) the incidence of sterility is sufficient to lower population recruitment and growth. Both conditions could, theoretically, be met by use of an infectious recombinant virus, expressing genes for specific reproductive antigens. Using the rabbit, I describe the research required to test the concept and discuss the legal and ethical consequences that may arise from a positive outcome to the research.

Keywords: Gamete antigens, population ecology, recombinant virus, risk assessment, social hierarchies

Introduction

The idea that fertility control has a potential for the management of wild species has been recognized in recent years, as shown by a 1990 meeting in Melbourne, Australia (Tyndale–Biscoe 1991) and a 1993 meeting in Denver, CO. While considerable support for this concept exists on grounds of humane control of wildlife, several important and as yet unresolved matters remain regarding its safety. The biological and ethical issues largely resolve into whether we are concerned with controlling populations of desirable species at appropriate levels with the option for reversing the effects in future years, or whether we are concerned to control populations of undesirable species of wildlife at very reduced levels indefinitely and at minimum cost. In North America, the first concern is the overriding one; in Australia and New Zealand, the second is.

The European wild rabbit, *Oryctolagus cuniculus,* is an excellent example with which to explore some of the biological and ethical questions surrounding the use of sterility as a means of management of wildlife. In some countries, it is a highly regarded wildlife species while in others it is the most serious and intractable of all pests (Thompson and King 1994). In addition, there are many other species of lagomorph around the world that are well regarded, and some are endangered (Chapman and Flux 1993). Clearly, methods developed for the control of the common rabbit must not affect these other relatives.

The rabbit is indigenous to southern Europe, where it is regarded as a desirable element of the fauna. In Spain, it is the main prey of eight raptors, two snakes, and six species of mammal, including the endangered lynx, and it is also a prized game animal. It was domesticated by French monks and taken by the Normans to Britain (Rogers et al. 1994). Domesticated varieties of the rabbit are raised throughout the world for meat, skin, and fur. It is also an important laboratory species, and there is a strong culture of breeding distinct varieties by rabbit fanciers. This range of interests in the rabbit involves a large and worldwide trade and distribution of rabbits and rabbit products. The nature of this interchange was dramatically demonstrated by the newly recognized rabbit calicivirus, which causes a rapidly fatal disease in rabbits (viral/rabbit hemorrhagic disease, VHD/RHD), after its discovery in China in 1984 (Liu et al. 1984) and its spread to southern Europe in 1988 and to Mexico in 1990.

In Britain, the long-term impact of the rabbit on vegetation was not appreciated until the demise of rabbits after the myxomatosis epizootic of the 1950's (Thompson 1994). Since the rabbit's subsequent recovery, the value of the damage rabbits now cause has been estimated at $180 million each year.

In the nineteenth century, the rabbit was released on many islands as a source of emergency food for castaways (Flux 1994), and it was also introduced by British colonists to Australia and New Zealand for a variety of reasons, including sentimental ones of enjoying the presence of a familiar animal in an alien country. In many cases, these introductions had severely deleterious consequences to the vegetation and indigenous fauna. In recent years, some of the islands under Australian and New Zealand control have been cleared of rabbits at very great expense (Burbidge 1989, Towns et al. 1990), and the vegetation is recovering. However, this is not a practical strategy for larger areas or for continental Australia.

The Rabbit Problem in Australia

Within 20 years of the introduction of rabbits to Australia, it was evident that they were a serious problem. Their explosive spread across the continent was complete by the early years of this century and resulted in gross overgrazing of the native grasslands, permanent degradation of the semiarid region, and widespread soil erosion. The long-term damage that the rabbit is doing in this large region of Australia is serious because it is preventing the regeneration of the long-lived plant species. When the old plants die, therefore, the whole ecosystem is irrevocably changed. The rabbit has been a major factor in the extinction of the small to medium-sized marsupials that were indigenous to this region and the value of losses to the pastoral industry each year has been estimated to be $500 million. The rabbit is acknowledged to be the most serious of all animal pest species in Australia and its control the most urgent.

In 1888, the Intercolonial Rabbit Commission was set up ". . . to rid the country of this menace." In the century since, many schemes to control the rabbit have been proposed, but only one has come near to accomplishing it. At the end of 1950, the myxoma virus was released. It spread rapidly across the southern half of Australia, causing massive mortality among rabbit populations. This was the single most effective control of a pest mammal ever achieved, and the effects of it are still apparent in most regions of Australia (Parer et al. 1985). Within a few years of the release, attenuated strains of the virus had evolved, and resistance to the virus had developed in the rabbit populations (Marshall and Fenner 1958, Fenner and Ratcliffe 1965). In order to counter this apparent decline in the effectiveness of the virus, the highly virulent Lausanne strain was imported from Europe and for 20 years was regularly released by land managers and owners for rabbit control. It probably caused high mortality at the site and time of each introduction but did not persist or spread very far. Recent evidence (P. J. Kerr, pers. comm.) suggests that the Lausanne strain has not displaced the preexisting strains, and its value for rabbit control is unclear.

The efficacy of myxoma virus for broad-scale rabbit control is critically dependent on insect vectors, and in Australia the initial epizootic was effected by two species of mosquito. In Europe, however, the spread of the virus was largely due to the rabbit flea, *Spilopsylla cuniculi*. In 1960, this species was introduced to Australia and has become an important additional vector in the higher rainfall regions of the continent. A third vector, the Spanish flea *(Xenopsylla cunicularis)*, which can survive in more arid environments, was released in South Australia in 1992. Hopefully, the Spanish flea will be an effective vector of the myxoma virus in the arid regions of the country, where rabbits are abundant in years of high rainfall.

Rabbit calicivirus was also being assessed in 1995 for possible release in Australia as another mortality agent. Unfortunately, it escaped from quarantine and is now widely dispersed. In addition to these measures, substantial resources have been directed by the Australian Government, through the Cooperative Research Centre for Biological Control of Vertebrate Pest Populations (1993, 1994), to investigate the potential for fertility control. In this approach, the myxoma virus would be used as a vector to introduce an immunocontraceptive to populations of wild rabbits.

Fertility Control of Rabbits

All previous attempts to control the rabbit have depended on developing methods to enhance mortality, such as disease, natural predators, commercial trapping, and shooting or poisoning with strychnine, arsenic, phosphorus, or sodium fluoroacetate (Compound 1080). Most of these methods are now illegal because of the pain they inflict on the animals in the process of killing them. In a recent study to compare the efficacy of these different methods, Williams and Moore (1995) found that the destruction of rabbit warrens was far more effective and long lasting than poisoning. When the warrens were left intact after fumigation or poisoning, rabbit populations recovered very rapidly because the warrens could be reoccupied and breeding could recommence. Similarly, after the initial highly successful reduction of rabbits in 1951–54 with the myxoma virus, rabbit populations recovered in some areas because warrens were left intact, reproduction of the survivors was not curtailed, and resistance to the virus thus evolved rapidly (Marshall and Fenner 1958). Clearly, the most important factor in rabbit control is the rate of recovery after a treatment has been applied: if that could be curtailed, as with warren ripping, the effect of all methods would be enhanced.

Fertility control is sometimes regarded as mortality applied at an earlier stage of the life cycle, but for many species it could be much more than this. Many studies on wild mammals have shown that reproductive success is closely linked to high rank in the social hierarchy of the population. Lower ranking animals either do not breed or fail to rear their young to independence (Wasser and Barash 1983, Abbot 1988). Failure to breed has been shown in wild foxes in Britain to be effected by the dominant members of the group (McDonald 1987). In the wild rabbit, there is no evidence that dominant females suppress breeding by subordinates, but the survival of the kittens of dominant females is significantly greater than for those of subordinate females (Mykytowycz 1959, Mykytowycz and Fullager 1973, Cowan 1987). Thus, sterilization of dominant members could affect fecundity of the population disproportionately, provided that the sterilized individuals remain sexually active and retain or improve their status in the social hierarchy of the population, and that a sufficiently high proportion of the population is sterilized (Caughley et al. 1992, Barlow 1994). While these conditions have long been recognized (Knipling 1959, Davies 1961), the problem has been how to achieve them for control of a wildlife species.

For many species with strong social structures, it is therefore important that a sterilizing agent not compromise the hormonal function of the gonads of the target animal. Because rank order is related to levels of sex hormones, a castrated animal is rapidly replaced in the social hierarchy and exerts little or no influence on the reproductive potential of other members of the population. Methods of fertility control that rely on exposing the target animal to steroids of one sort or another usually affect endocrine functions and consequently the sexual and social behavior of the animal (Bomford 1990 and this volume). Likewise, the use of agents that immunize the animal against gonadotropin hormone-releasing hormone (GnRH) or block receptors for GnRH in the pituitary seriously affect the steroidal functions of the gonad as well as its gametogenic function. While these methods have wide application in livestock management, and could be useful for the control of breeding in local populations of wildlife or for those species in which breeding suppression does not occur, they are of little potential use for pest species where social and sexual behavior must not be compromised. Agents that affect gametes, fertilization, or implantation must be sought and then presented to the target animal in such a way as to induce a strong and persistent immune response that prevents or compromises pregnancy.

A second requirement for a widespread pest species like the rabbit is a means of delivering the agent to a large proportion of the population. The concept that we are investigating for the rabbit is to clone the genes encoding proteins that are critically involved in fertilization or implantation and insert them into the myxoma virus. Rabbits infected with the recombinant myxoma virus would simultaneously raise antibodies to the virus and to the reproductive antigen, and fertilization or implantation would be prevented. Because this immunization would not affect the hormonal status of the rabbit, it would not affect its sexual activity or social status in the population. For the wild rabbit, five key questions derive from this concept:

1. What proportion of females in a wild population must be sterile in order to reduce significantly the rate of growth of the population?

2. Can gamete-specific proteins be presented to the animal in such a way as to provoke an effective and long-lasting immune response that interferes with fertilization or fetal development?

3. Can recombinant myxoma viruses that express the genes encoding the gamete proteins be constructed in such a way that they can act as vectors to

immunosterilize the proportion of the wild population identified in the first question?

4. How and when will selection forces diminish the effect of the recombinant virus?

5. Can this be achieved in a way that does not put at risk other species in Australia or rabbits in other countries?

Effects of Sterility on Rabbit Population Dynamics

In Western Australia and in New South Wales, two large experiments on wild rabbits were begun in 1993 to test the effect of sterilizing various proportions of the female population on rate of increase and survival of young. In each experiment, 12 free-range populations, each initially of 50 to 100 adult rabbits, were isolated by combinations of fences and buffer strips, and each was allocated randomly to 1 of 4 treatments. On each site, all the rabbits were caught and marked, and 80 percent of the adult females were subjected to surgery, either laparotomy or ligation of the oviducts. The proportions sterilized on three sites each were 0 percent, 40 percent, 60 percent, or 80 percent. In addition, the impact on the European flea, *Spilopsyllus cuniculi,* and the incidence of infection with myxoma virus are being investigated. This flea is being studied because its life cycle is intimately tied to the reproductive cycle of the rabbit, particularly females in late pregnancy and newborn kittens. With a high proportion of the females sterile, will the flea population be able to survive and transmit myxoma virus?

These experiments have been run for 3 years to determine how the productivity of the populations is affected by the different levels of sterilization. Preliminary results from the first year suggest that, while the number of kittens was reduced on sites where females were sterilized, survival of these kittens was higher than on the control sites, so that, by the start of the next breeding season, the net production between sites was not different. However, survival of sterilized females appears to have been higher than for intact females and males, and sterilized females entered the next breeding season heavier than intact females (Williams and Twigg 1996). In the second and third years, the treatments were repeated on new recruits to the populations. In both experiments, climatic vagaries during the 2 years affected reproduction and survival. In general, however, the effect of sterilization followed the pattern of the first year. The most notable result was that the higher levels of sterility reduced the annual cohort of recruits; populations with 80-percent sterility tended to have a flat trajectory over time, unlike the fluctuating pattern in the experimental controls (L. Twigg and C. K. Williams, pers. comm). Knowledge of the longer term effects of sterility must await detailed analyses of these experiments and their application to mathematical models for extrapolation. This information will be crucially important in deciding the requirements for an effective recombinant virus.

Gamete Antigens for a Rabbit Immunocontraceptive

Effort is presently concentrated on interfering with fertilization by identifying those proteins present on the surface of the sperm and the ovum, which are involved in the processes leading to fusion of the male and female nuclei. These are

(1) locomotion of the sperm, which brings it into the vicinity of the of the ovum;

(2) the first contact between the sperm head and the zona pellucida, which induces the acrosome reaction of the sperm;

(3) release from the acrosome of enzymes that break down the zona and allow the sperm to pass through and lie against the plasma membrane of the ovum; and

(4) proteins on the equator of the sperm head that are thought to be critically important in causing the fusion of the sperm and egg plasma membranes, so that the sperm nucleus can enter the egg and fuse with its nucleus.

The approach being used to identify and isolate selected antigens is to develop polyclonal and monoclonal antibodies to gamete antigens and, if possible, assess the effect of these antibodies on sperm–egg binding, on in vitro fertilization, and on fertility in intact animals.

To date, 35 monoclonal antibodies have been prepared against rabbit sperm, and some of them have been shown to block sperm–egg binding and prevent fertilization in vitro. A cDNA library has been prepared from rabbit testis, and the gene encoding for one of these proteins (Pop1) has been sequenced and appears to be a novel testis-specific protein (M. Holland, pers. comm.). In addition, DNA probes, derived from sperm antigen genes of other species, are being used to isolate the rabbit homologues from the rabbit testis cDNA library. The first of these to be characterized are the homologues of the genes for the guinea-pig sperm antigens PH20 (Holland et al. 1997) and PH30 (Hardy and Holland 1996).

For effective immunocontraception, the antigen must provoke a strong and sustained immune response that will interfere with the functions of the gametes. This process involves the appropriate presentation of the antigen to the immune system to induce strong memory and the development of high titres of appropriate antibodies at the time that fertilization is most likely to occur. Gamete antigens are self proteins and therefore may not induce a strong immune response alone. However, spermatozoa, which are normally not presented to the immune system of the male because of the blood–testis barrier, may provoke an immune response when presented to the systemic circulation of males.

Effective application of a vaccine for fertility control requires that a high level of immunity be achieved amongst individuals exposed to the vaccine. In outbred populations of wild mammals, heterogeneity of the immune response between individuals may make it hard to reach or sustain that level. It may therefore be necessary to include several antigenic determinants together, so as to stimulate a broad range of immune responses within the population. In addition, the antigen(s) may have to be presented in conjunction with other highly immunogenic carrier proteins in order to induce a strong and lasting immunity. This could include species-specific cytokines, such as interleukin–6, which has recently been shown to enhance the immune response in vivo in mice (Ramsay et al. 1994).

Molecular Virology and Antigen Delivery

For immunosterilization to be effective in a wild population, the gamete antigens must reach a large proportion of the exposed population. Delivery systems can utilize

(1) direct presentation of the antigen (in baits or by projectiles, which is costly but safe),

(2) oral administration of nondisseminating recombinant micro-organisms (which carry the genes encoding the gamete antigens and immunogenic carrier proteins), or

(3) a recombinant micro-organism that spreads through the target population by sexual transmission, contagion, or arthropod vector.

The delivery of immunosterilizing agents by bait has considerable value in circumstances where the target population is restricted in distribution or in time. However, the control of rabbits in Australia calls for a more cost-effective means of delivery that would spread the agent through the population independently. This of course, brings with it a much higher degree of risk—but not so high that the concept should not even be investigated or contemplated.

Over the past decade, recombinant viruses, carrying gene sequences derived from other organisms, have been constructed to function as living vaccines. The best example is the vaccinia virus recombinant expressing a portion of the rabies virus genome, which has been used very successfully in Europe to immunize populations of wild foxes (Brochier et al. 1990). The success of this project is due to the ability of the recombinant virus to replicate in the oral cavity of the infected fox and because the rabies glycoprotein expressed by the inserted gene is highly immunogenic.

The myxoma virus has been circulating in the rabbit populations of Australia for more than 40 years, and no evidence has been found to indicate that it infects species other than rabbits. Myxoma virus is a large DNA leporipoxvirus, related to vaccinia virus, so technologies already developed for preparing recombinant poxviruses can be adapted for the construction of recombinant myxoma viruses. During the past 9 years, the structure of the virus genome has been investigated (Russell and Robbins 1989), and a number of open reading frames in the central region of the genome have been identified (Jackson and Bults 1990 and 1992a, R. J. Jackson et al. 1996), including insertion sites homologous to those used in the vaccinia virus work. The aim here was to preserve the viability and infectivity of the native myxoma virus by inserting foreign DNA at intergenic sites, and not to compromise the virus by inserting foreign DNA intragenically.

Plasmid transfer vectors, based on the myxoma virus, have been constructed. These vectors contain a multiple cloning site adjacent to vaccinia virus promoter elements inserted in an intergenic region between the myxoma virus *tk* gene and open reading frame MV8a (Jackson and Bults 1992b). These vectors were used to generate recombinant myxoma viruses in cell culture and demonstrated that the myxoma virus can carry additional DNA and express the product in a culture system (Jackson and Bults 1992b), and without associated attenuation (R. J. Jackson et al. 1996).

Other recombinant myxoma viruses have been constructed using an attenuated strain, which express the hemagglutinin antigen of influenza virus (Kerr and Jackson 1995). These recombinants express cell-membrane-bound hemagglutinin, which can be detected by immunofluorescence. In live rabbits, the recombinants provoke strong antibody titres to the myxoma virus and very strong antibody titres to the hemagglutinin antigen. This demonstration opens the way for the insertion of other genes, such as those encoding for reproductive antigens.

Competition Between Recombinant and Native Strains of Virus

Concurrently with the reproductive and viral programs, it is important to determine the conditions under which dissemination of the recombinant virus, expressing sterilizing genes, may be able to outcompete existing field strains. To assess such potential competition, the pathogenesis and epidemiology of the recombinant virus must be compared to that of purified strains of the virus and, in the case of myxoma virus, the various field strains that have evolved over the past 40 years in Australia. Using the techniques of restriction length fragment polymorphism and polymerase chain reaction, P. J. Kerr (pers. comm.) has been able to identify field strains of myxoma virus by criteria that are independent of the virulence or pathogenesis of the strain. This work is not only providing a far greater appreciation of the regional differences in the virus and its host but will enable the selection of strains with which to prepare recombinants much more effectively targeted to rabbit populations.

The other question here is the fitness of the sterilizing recombinant virus to survive in the host population. In preliminary modelling for a recombinant myxoma virus expressing a sterilizing gene, being undertaken by R. Pech and G. Hood (pers. comm.), persistence of strains depends on the rate at which new susceptible rabbits enter the population. Even virulent strains can persist in the population if the birth rate is high; at lower birth rates, however, only avirulent strains with a long period of infectivity survive. The persistence of sterilizing strains may be even more constrained because there will be fewer opportunities for transmission to new, susceptible rabbits. In a different model, in which the sterilizing virus is assumed to be sexually transmitted and to persist in the infected host, Barlow (1994) has estimated that the recombinant virus will be at a selective advantage over the native strain because the more frequent return to estrus by sterilized females will provide more opportunities for transmission. In this situation, he concludes that the recombinant virus could persist in a population that stabilizes at a substantially lower level.

Legal and Ethical Issues of Viral-Vectored Immunosterilization

The development of immunosterilizing vaccines that can be delivered to wild animals raises a number of important issues about the international consequences of the impact of an agent designed for a species that is a pest in one country but a desirable or even endangered species in another. One view is that the outcome of the concept is so uncertain and the risks are so great that approval for release will never be given; therefore, the research should not proceed at all. Implicit in this view is the inference that these other issues will always outweigh the problem of the rabbit in Australia, a problem of great magnitude. An opposing view, which we favor, is that the research should proceed incrementally with public discussion and proper scrutiny at each step, so that, if the concept is shown to be valid, its potential use can be assessed properly against the risks. This view recognizes that understanding of the control processes in gene expression is advancing so fast that difficulties that now seem insuperable may not be so in a few years. However, if we wait until then before embarking on the basic research required to develop the concept, we will have delayed the time when it can be used. Delay may lead to further deterioration of threatened ecosystems, which is an issue of great concern in Australia. The debate is just beginning, and it is too early to establish rigid directives on this matter. Rather, it is important to establish first, whether it is possible to control populations by immunosterilization and second, if it is, to explore the range of options for delivery of the immunogen. Options range from the direct delivery of a nontransmissible immunogen, which is costly but has a low risk, to delivery by a disseminating microorganism in which the unit cost is very low but the risk is higher.

The risks relate to (1) the effect on species other than the prime target in the country with the pest problem, which are primarily national risks, and (2) the risks to the target species and related species in another part of the world, where they are valued highly. The latter risks are mainly international.

National Aspects—The important questions relate to species-specificity of the reproductive antigen complex, specificity of the virus to be used as the vector, and specificity of the means by which it will be transmitted.

Gamete antigens that have been characterized in recent years show considerable homology between species at the genomic level, and researchers need to know whether antigenic epitopes can be identified that affect fertilization only in the target species. It is likely that such epitopes, if they exist, may not provoke a strong immune response by themselves but may do so when coupled with some other protein or when expressed in conjunction with cytokines. If the cytokines themselves are specific to the target species, both specificity and immunogenicity of the antigen would be enhanced. Alternatively, if species-specific gamete antigens cannot be identified, then other antigens involved in reproduction may need to be considered. In the case of the rabbit, the protein uteroglobin, which is associated with implantation (Beier 1982), is specific to the rabbit and the gene encoding it has been cloned (Bailly et al. 1983). However, the evidence that it is essential for implantation is not strong, and the case against gamete antigens would have to be very strong before attempting to exploit uteroglobin for immunosterilization.

In the choice of vectors for the delivery of sterilizing antigens, the important aspect is the degree to which the viral vector is specific to the target species and is incapable of replicating and provoking an immune response in nontarget species. For myxoma virus in Australia, the case is strong that it is specific to the rabbit. In the past 40 years, as mentioned earlier, no evidence has been produced to indicate that the virus affects any species other than the rabbit, and humans exposed in an outbreak of myxomatosis did not seroconvert (E. W. Jackson et al. 1996). However, no critical tests have been done to determine that it does not undergo minimal replication in nontarget species, and no nontarget species has yet been screened for seroconversion. That can now be done for myxoma virus, using an enzyme-linked immunosorbent assay (ELISA) developed in our Center (Kerr 1997).

The third level of specificity is the way in which the virus is conveyed from one member of the target species to another. Contagious or insect-borne transmission involves a risk of cross-species infection, unless the insect vector is specific to the target species. Neither of the two species of rabbit flea introduced to Australia feeds on species of vertebrate other than the rabbit, and *Spilopsyllus cuniculi* can complete its own life cycle only on rabbits. However, the myxoma virus can be transmitted by other biting insects, a fact that reduces its specificity. Transmission of a viral vector by sexual contact or placental transfer would confer the greatest degree of specificity. In polyestrous species, sexual transmission would also confer a selective advantage on the recombinant over the native virus because, as mentioned above, females infected with the recombinant would undergo estrus more often and hence provide more opportunities for virus transmission (Barlow 1994). In this regard, herpesviruses that are sexually transmitted, show persistent infection, and are species specific may be particularly suitable candidates as viral vectors (Shellam 1994).

International Aspects—Another major concern about immunosterilization is international, centering on the risk posed by immunosterilization to a target species in countries where it is indigenous and well regarded. The concern is the risk of accidental or malicious export of the agent from a country where it is used for pest control to another country. For the rabbit, these concerns relate not only to the impact that the recombinant virus might have on *Oryctolagus cuniculus* but on other leporids that are susceptible to infection with leporipoxviruses. In North America, there are 17 species of *Sylvilagus* that could be infected, some of which are considered to be endangered species (Chapman and Flux 1993). In addition, there are other rare leporids in Mexico, Indonesia, and Japan that might be susceptible. The International Union for Conservation of Nature/Status Survey and Conservation Lagomorph Specialist Group has expressed strong reservation about the use of genetically engineered myxoma virus because of the potential risk to these species. What steps would be required to address this strongly expressed concern? A risk assessment needs to be undertaken that would place probability values on (1) transfer from the user country, (2) establishment in a second country, and (3) means to contain its spread, should an outbreak occur. These are similar to the concerns of international agencies that currently deal with other infectious organisms.

Probability of Transfer From the User Country—This probability would only include accidental or illegal transfer because presumably the power of legislation and its implementation with regard to the export of micro-organisms would be exercised under current international obligations. If the user country were Australia and a recombinant myxoma virus were being considered, risk assessment should include the past history of the virus in the country, the conditions required for initial establishment of the virus, and the evidence, if any, of the occurrence of genetically identifiable Australian strains of the virus anywhere else. The present evidence is that Australia is the only country that used the Standard Laboratory Strain (SLS) of the myxoma virus, and all field strains in Australia appear to be derived from it (P. J. Kerr, pers. comm.). There is no evidence that any strain of myxoma virus from Australia has been deliberately or accidentally spread to any other country. With techniques now developed, it would be possible to determine whether SLS-derived strains of the virus occur elsewhere.

It is perhaps significant that several attempts to release the virus in Australia before 1950 failed. The successful outbreak was due to the coincidence of widespread rains and large populations of two species of mosquito (Fenner and Ratcliffe 1965, Fenner and Ross 1994). In the early 1950's, attempts were also made to introduce the SLS myxoma strain to New Zealand, but they failed. At the time, investigators concluded that this happened because the appropriate insect vectors were not available to transmit the virus (Gibb and Williams 1994). More recently, there were moves to introduce the rabbit flea to New Zealand so as to provide a suitable vector, but the New Zealand Government decided in 1993 to forbid the release of the flea and the virus. There are several potential insect vectors of myxoma virus in New Zealand and many people there who would like to see the virus used. Despite this, legislative controls have been a sufficient barrier to its entry for 44 years.

Probability That the Agent Could Become Established in a Country Where the Target Species or Related Species Are Endemic—Whether leporipoxviruses are already present in the nontarget populations would influence whether the new virus could become established. Where related viruses or the same virus is already present, the probability of the recombinant strain becoming established may be low because of the so-called founder effect and also because genetic manipulation may render the recombinant less competitive. In Australia, despite massive and repeated release of the Lausanne strain since 1957, particularly in Victoria (Fenner and Ross 1994), all field isolates so far examined are genetically derived from SLS (P. J. Kerr, pers. comm.). This finding suggests that the Lausanne strain has been unable to establish in the face of preexisting strains. In an analogous way, Japanese B encephalitis flavivirus has never become established in Australia, where Murray Valley encephalitis virus occurs, despite annual introductions in migratory birds from Japan (Davey et al. 1982).

In Europe, where the Lausanne strain of myxoma virus was released, it underwent a parallel but wholly independent evolution of attenuation (Fenner and Ross 1994). If the founder effect applies to virus strains, Australian SLS-derived strains would be unable to establish in Europe. This idea could be tested on Macquarie Island, where Lausanne was the only strain released, by introducing genetically distinct SLS strains.

The same principle applies to establishment of an immunosterilizing virus in Australian wild rabbit populations. Competition with field strains probably will pose a severe barrier to introduction and transmission, and special strategies for seeding and timing will probably need to be adopted. Such conditions would suggest a very low probability of transmission by limited events, such as accidental or malicious release in another country. Nevertheless, if research enables a highly competitive immunosterilizing strain to be produced and/or foreign populations or species are shown to be at risk, careful consideration must be given to the strains used and the safeguards to be built into the genetic manipulations and to whether these safeguards would provide adequate protection.

In America, various strains of myxoma virus are endemic in species of *Sylvilagus* in the Western United States and several countries in Central and South America, but the incidence of seropositivity in wild populations has been determined in a limited way for *S. bachmani* in California only (Regnery and Miller 1972). This strain was shown to be capable of infecting four other species of *Sylvilagus,* but it could not be transmitted by mosquito from any of the primary hosts because the amount of virus was insufficient for effective mosquito transfer (Regnery and Marshall 1971). A more extensive assessment of this would be required to develop probabilities of a recombinant strain becoming established. Laboratory testing of susceptibility to infection and transmission would determine whether the risk is real for these other species and so contribute to assessment of their magnitude. In other parts of the world, where leporipoxviruses do not occur, the susceptibility of rare leporids might have to be determined.

Develop Means To Contain Its Spread, Should an Outbreak Occur.—From the foregoing, the probability of an outbreak spreading in a population of rabbits that are already exposed to leporipoxvirus is low. However, in a naive population the myxoma virus can spread rapidly, as occurred in Europe in 1952 (Fenner and Ross 1994). If other leporids are shown to be susceptible to the virus and there was deemed to be a risk of transfer of the immunosterilizing virus, contingency plans would have to be considered. In Australia, contingency plans have been developed for containing an outbreak of major diseases of domestic stock, such as foot-and-mouth disease virus in feral pigs (Pech and McIlroy 1990), and similar models could be developed for myxoma virus. The important factor is to recognize the outbreak at an early stage and to reduce the proportion of susceptible animals rapidly, either by destroying them or by immunizing them against the pathogen. In the case of myxoma virus, there are now several isolates of the virus that are attenuated but immunogenic. P. J. Kerr (pers. comm) is currently investigating the genetic basis of pathogenesis and virulence using these isolates. These studies may provide strains of the virus that could be used to deliver broad-scale immunization to contain an unwanted outbreak. In California and in France, highly attenuated strains of myxoma virus have been developed as vaccines to protect domestic and wild *O. cuniculus,* but attempts to produce an inactivated myxoma virus vaccine have been unsuccessful (Fenner and Ross 1994).

Conclusion

Effective control of pest mammals is immensely difficult. While current methods using specific disease organisms or poisons may have some benefit, it is widely acknowledged that none has long-term promise. So far as poisons are concerned, there is doubt even of their medium-term efficacy. A new approach to pest animal control is urgent; the concept of a viral-vectored immunosterilant is such an approach. Because it is novel, the outcome is uncertain, and the risks are considerable. However, if the risks can be reduced to an acceptable level and this methodology is effective in controlling rabbits, the benefits will be very great. Furthermore, because the concept is generic, if it is effective in this species, it has the potential to be applied to other species as well. Three species are already being investigated—the European red fox, *Vulpes vulpes* (Bradley, this volume), and the brushtail possum, *Trichosurus vulpecula* (Jolly, this volume), in New Zealand; and the wild house mouse, *Mus domesticus* (Shellam 1994), in Australia.

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The Development of Contraceptive Methods for Captive Wildlife

Cheryl S. Asa

Abstract: Contraception has become critical in managing zoo populations, both to limit production of surplus animals and to promote genetic health. One role of the Contraception Advisory Group, formed in 1989, is to coordinate research to develop new contraceptive methods. Because melengestrol acetate (MGA) implants, which have been used by zoos for almost 20 years, recently have been associated with uterine pathology in felids, several new contraceptive techniques are being evaluated. These include other steroid hormone formulations, such as the birth control pill Depo-Provera,® the Norplant® implant, and MGA added to feed; bisdiamine, an oral male contraceptive; zona pellucida (ZP) vaccine; and vas plugs. Bisdiamine reversibly blocked spermatogenesis while sparing testosterone in its first test in gray wolves. ZP vaccine has been effective in preventing births in a variety of species of hoofstock, primates, and carnivores; however, long-term deleterious effects on the ovaries have been found in some controlled trials. Injectable vas plugs that conform to the shape of the vas make it possible to successfully treat a wide variety of species; reversal trials are currently underway. As research efforts continue, we hope to expand our collaborations with scientists working on contraceptive development for humans, companion animals and wildlife, to better make use of the limited resources available for these investigations.

Keywords: contraception, captive animals, zoo, vas plugs, bisdiamine, indenopyridine, zona pellucida vaccine, GnRH agonist, LHRH vaccine

Introduction

The modern zoo now faces the consequences of becoming too successful at breeding and maintaining the animals in its care. Advances in husbandry, nutrition, and medicine have resulted in more births and longer lives for most captive species. The major benefit of this success is that these captive populations can be self-perpetuating and not dependent on importation of animals from the wild. However, due to limited space and resources, zoos cannot allow uncontrolled reproduction.

In addition, zoos give high priority to proper genetic management, that is, reduction of inbreeding and balanced genetic representation of the founders of captive populations. Both genetic management and limiting production of surplus animals are being accomplished through contraception.

Although physical separation of males and females can prevent unwanted conceptions, most zoos consider this an undesirable measure. Not only can such an arrangement be stressful for species in which males and females typically associate, lone animals present an unnatural view of that species to the visiting public. A primary mission of zoos is education, a mission that is better served by maintaining animals in social groupings which are as representative as possible of the organization that would occur in the wild.

In recognition of the importance of contraception in responsible animal management, the American Association of Zoos and Aquariums approved formation of the Contraception Advisory Group in 1989. Composed of zoo curators, veterinarians, and reproductive physiologists, the group surveys the use of contraception in zoos for inclusion in a computerized data base, advises zoo personnel, and initiates and coordinates research into alternative methods.

The International Wildlife Contraception Database, housed at the St. Louis Zoo, was developed and is maintained by Ingrid Porton and Betsy Hornbeck of the Contraception Advisory Group. Begun in 1990 and updated from yearly surveys, it currently contains more than 2,000 complete records on 184 species and serves as a resource for zoo animal managers and for researchers.

Contraception of captive wildlife in zoos began in the mid-1970's. After preliminary tests with lions and tigers (Seal et al. 1976, Seal and Plotka 1978) comparing medroxyprogesterone acetate (Provera,® The Upjohn Co., Kalamazoo, MI, USA) and melengestrol acetate (MGA, also Upjohn), MGA in silicone implant form was selected as the more suitable. Of the more than 80 percent of North American zoos that reported using contraception (Porton et al. 1990), most use the MGA implant.

However, concern has arisen about possible pathology in progestin-treated carnivores (Kollias 1988, Kollias et al. 1984) because deleterious effects have been associated with progestin use in domestic dogs and cats (reviewed in Asa and Porton 1991, Asa et al. 1996). Indeed, histological examination of uteri from MGA-treated felids has revealed significantly more pathology than those from untreated felids (Munson and Mason 1991).

No comparable effects are expected in primates, based on the extensive studies that have been conducted in laboratory primates, as well as decades of progestin administration to human females. In general, birth control methods that have been approved for human use should be safe and effective for nonhuman primates. Birth control pills (combination progestin and estrogen, various formulations commercially available), Depo-Provera, Norplant (levonorgestrel implant system, Wyeth–Ayerst, Philadelphia, PA, USA), and intrauterine devices have been used in primates, especially in the great apes (Porton et al. 1990). However, few data exist on progestin effects in ungulates and other mammals.

A number of research trials are under way to evaluate new approaches with the hope of providing a broader selection of contraceptives, especially alternatives to the progestin-based formulations for carnivores. These include vas plugs, the antispermatogenic compounds bisdiamine and indenopyridine, and short-term Depo-Provera for seasonal breeders. Additional work is focusing on specific aspects of MGA treatment. For a discussion of the progress of zona pellucida trials in zoos, see Kirkpatrick et al., this volume.

Melengestrol Acetate

As mentioned, MGA is the most frequently used contraceptive for captive mammals. MGA is incorporated into silicone rods by E. D. Plotka (Marshfield Medical Research Foundation, Marshfield, WI) and distributed to zoos throughout the world. When inserted subcutaneously, the implants provide effective contraception for at least 2 years (Porton et al. 1990). The only side effect noted in primates has been weight gain (Portugal and Asa 1995), which is also common in human females treated with progestins.

Because of concern about possible effects on social behavior, a study was conducted with a troop of hamadryas baboons *(Papio hamadryas)* at the St. Louis Zoo (Portugal and Asa 1995). Administration of MGA was not associated with social disruption. Treated females were involved in fewer affiliative interactions, but there was no increase in aggression compared to control animals.

Although MGA implants have been effective in a wide range of monkeys and apes, some New World primate species have proven resistant. Because they have naturally high levels of endogenous steroids, these species may require larger exogenous doses to achieve contraception. Research is being conducted to test this hypothesis (E. Plotka, pers. comm.).

Recognizing that individual capture and immobilization for implant insertion may be inadvisable in some situations, Bronx Zoo veterinarians (B. Raphael, pers. comm.) have tested adding MGA to feed for herds of antelope and deer. Although this procedure is generally successful, drawbacks include contraceptive failure in some subordinate animals that apparently did not ingest a sufficient dose and alteration of the antler cycle in male barasinga *(Cervus duvauceli)*.

Pathological effects of MGA and related progestins are being investigated by Linda Munson (University of Tennessee, Knoxville). Early work concentrated on reproductive tracts of felids (Munson and Mason 1991), and research is now extending to other carnivores and primates. In general, progestins have been found to stimulate growth of the uterine lining of felids and canids, resulting in hyperplasia, pyometra, and neoplasia (reviewed in Asa and Porton 1991). Effects of dosage, length of treatment, and age during treatment are currently being studied.

Depo-Provera

The belief that side effects can be minimized by a shorter treatment period has created interest in the progestin medroxyprogesterone acetate in its injectable, slow-release formulation. In particular, seasonal breeders that are fertile for only part of the year might benefit from progestin exposure for only that period, as opposed to the continual, long-term exposure imposed by an implant. An injection every 2–3 months is thought to be preferable to the repeated surgical procedures required for implant insertion and removal.

Dose/response trials and evaluation of weight gain have been conducted with ruffed lemurs *(Varecia variegata)* and black lemurs *(L. macaco)* at the St. Louis Zoo, in collaboration with the Henson–Robinson and Metro Toronto zoos. Using vaginal cytology to monitor suppression of cycles, researchers found the minimum effective dose to be 5 mg per kilogram of body weight. Pelage darkening in treated black lemur females was an unexpected side effect, probably related to the ability of this progestin to bind androgen receptors (Labrie et al. 1987). (Black lemurs are sexually dimorphic in color, with males having a black and females a brown coat).

Depo-Provera also is being used in hippopotamuses *(Choeropsis liberiensis),* giraffes *(Giraffa camelopardus),* sea lions *(Zalophus californianus),* and gray seals *(Halichoerus grypus),* although not part of controlled research projects. There is concern about sea lions and seals, in particular, because they are closely related to the carnivores and because they have extensive fat stores that may absorb and hold steroids, which are lipophilic. Fat stores may also present a problem with hippos.

Norplant

Although no controlled studies have been published, several zoos are using these implants, which contain levonorgestrel, a synthetic progestin related to both MGA and Provera. Its advantage over MGA is the much thinner capsules, which can be inserted with a trocar. Compared to the incision and sutures needed for the MGA implants, the small puncture site attracts less grooming and reduces the chance of loss.

Birth Control Pills

As with Norplant, some zoos opt to use oral birth control pills, another product developed for the human market. The willingness of many apes to take pills placed in food treats dispenses with the need for immobilization and insertion of an implant. The vast majority of pills contain estrogen in combination with a much lower dose of progestin than is present in the progestin-only forms discussed above. Although this combination does not significantly alter the associated side effects for primates, it is not appropriate for carnivores. Adding estrogen to progestin in formulations given to dogs exacerbates uterine pathology (Teunissen 1952).

Megestrol Acetate

Another synthetic progestin—available as Megace® (Mead Johnson Laboratories, Evansville, IN, USA) or Ovaban® (Schering–Plough, Union, NJ, USA)—is sometimes used as a contraceptive in domestic dogs and cats. However, because of the attendant risk of hyperplasia and pyometra, this synthetic it is not recommended for more than two consecutive treatments.

Lupron Depot®

An agonist of GnRH (gonadotropin-releasing hormone also called LHRH, luteinizing-hormone releasing hormone), Lupron Depot (TAP Pharmaceuticals, North Chicago, IL, USA) has been used in males of several species in attempts to block spermatogenesis. Although theoretically tenable, this approach has been unsuccessful due to incomplete suppression of sperm production. Sperm numbers must be reduced below the level required for fertilization for this to be an effective contraceptive. Because the GnRH agonists and antagonists block production of testosterone, they also can find application in suppression of aggression in some individuals.

Lupron Depot also has been given to females to suppress cyclicity. However, because agonists first stimulate the endocrine cascade that results in ovulation, administration to induced ovulators, such as the felids, may stimulate ovulation and pseudopregnancy before suppressing cycles by negative feedback.

Although analogues show promise in providing the equivalent of reversible chemical castrations, their current cost prohibits for widespread use. Long-term delivery also is a problem. Because these compounds are not orally active and do not follow the same diffusion dynamics as steroids, traditional delivery methods such as silicone implants have not been effective. Both a silicone elastomer matrix and a reservoir system are being tested (Vickery et al. 1989).

LHRH Vaccine

Immunization against LHRH can provide contraception for both males and females (Fraser 1986). LHRH initiates the cascade of hormonal events that results in testosterone and sperm production in males and in production of estrogen and progesterone and ovulation in females. Because this vaccination would accomplish the equivalent of a reversible chemical castration, it can be especially appropriate for males to suppress testosterone and thus aggression and for female carnivores to completely suppress secretion of progesterone. Vaxstrate, an LHRH vaccine that is commercially available in Australia (Arthur Webster Pty. Ltd., New South Wales, Australia) for domestic cows (Hoskinson et al. 1990), has also been used with success in some exotic species at the Western Plains and Perth zoos (D. Blyde and S. Haigh, pers. comm.). In this country, both The Population Council in New York and Colorado State University are developing LHRH vaccines.

Bisdiamine

All the steroid hormone preparations in use in zoos target the female. However, if prevention of reproduction is desired in polygynous social groups, it is more efficient to treat the males than the females. The bisdiamine WIN 18,446 (Sterling Winthrop, Rensselaer, NY, USA) was tested in the early 1960's as a birth control pill for men. It works by selectively interfering with spermatogenesis but not testosterone production. Although initial trials demonstrated the drug to be effective, safe, and reversible, it was soon discovered to interact with an enzyme that detoxifies alcohol. Thus, men taking bisdiamine who then drank alcohol became ill, making the compound unsuitable for general marketing. Because we assume that we can prevent alcohol consumption in captive animals, bisdiamine may be a feasible contraceptive alternative for this application.

The first test of bisdiamine in a wildlife species was conducted with a captive colony of gray wolves (Asa et al. 1995). Daily administration in ground meat at a dose of 200 mg/kg suppressed spermatogenesis without affecting mating behavior. In the subsequent breeding season, semen samples of the previously treated males were comparable to those of controls, confirming reversibility.

Indenopyridine

This drug (Research Triangle Institute, Research Triangle Park, NC, USA) is similar to bisdiamine in that it is orally active and blocks sperm production without interrupting testosterone secretion. To date, it has been tested only in rodents (Fail et al. 1991, Gurtler and Donatsch 1979, Hodel and Suter 1978), so the extent of its efficacy and safety has not been adequately determined. A dose response trial with domestic cats, as a model for exotic felids, is currently being conducted (Fail et al., unpubl.)

Vas Plugs

L.J.D. Zaneveld and I investigated vas plugs. Silicone injected into the vas deferens, the tube carrying sperm from the testis, hardens to form a barrier that prevents the passage of sperm. Plugs were placed in 59 mammals, including marsupials, felids, primates, and ungulates, at 17 different zoos. Early use of the preformed plug (Zaneveld et al. 1988), which is also in clinical trials with humans, proved inadequate for the range of vas sizes encountered in zoo animals. The injectable plugs were successful in blocking passage of sperm, but fertility was not restored after removal.

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Haigh, Stephanie. Perth Zoo, South Perth, Western Australia.

Plotka, Ed. Marshfield Medical Research Foundation, Marshfield, WI 54449, U.S.A.

Raphael, Bonnie. Animal Medical Center, Bronx Zoo, New York, NY 10460, U.S.A.

Contraception in Wildlife Management: Reality or Illusion?

David C. Guynn, Jr.

Abstract: Nuisance wildlife in areas where hunting is not an accepted practice and declining public support of lethal control measures have prompted research on contraceptives as a way to manage population levels. However, complex legal, biological, economic, and ethical issues should be addressed before such techniques are tested even on small, isolated populations. Regulatory authority by State and Federal agencies must define protocols for using contraceptive materials in wild populations. Registration of wildlife contraceptives either as pesticides or vaccines will likely be necessary. Health-related issues include harmful effects on target species, nontarget species and humans who may consume carcasses. Models for evaluating population impacts and genetics are needed. Cost effectiveness itself and who will pay these costs must both be considered. Disruption of behavioral mechanisms and resulting population impacts raise ethical considerations. Contraception may have application with limited, isolated or confined populations, but its eventual use on free-ranging wildlife populations is questionable.

Keywords: Wildlife contraception, State and Federal regulations, impacts on animal behavior

Nuisance wildlife, particularly high densities of white-tailed deer *(Odocoileus virginianus),* have become a problem in many areas of the United States (Warren 1991). Significant economic losses can result from damage to crops and landscape plantings and from deer–vehicle collisions. Regulated hunting can be an effective means of controlling deer populations (Behrend et al. 1970). However, problems in areas where hunting is not an accepted practice (e.g., national parks and suburban areas) and declining public support of lethal control measures have prompted research on contraception as a means of managing population levels. Recent studies on immunocontraception of free-ranging feral horses *(Equus caballus)* (Goodloe 1991, Kirkpatrick and Turner 1991) and deer (Turner et al. 1992, Warren and White 1995) indicate that an effective vaccine and oral delivery system could be developed. However, complex legal, biological, economic, and ethical issues should be addressed before such techniques are applied even on small, isolated populations. This chapter will attempt to identify some of the key points of these issues with focus on management of white-tailed deer.

Legal Issues

Although wildlife contraception is a potential management tool, contraception research is being conducted outside of the State and Federal agencies having primary responsibility for management of wildlife populations. Except for migratory species and species afforded protection under the Endangered Species Act, the State wildlife and fisheries agencies are empowered to manage wildlife populations. Each State has a unique set of statues and regulations defining legal utilization and protection of wildlife to include status as a hunted or nonhunted species, season lengths, bag limits, baiting and feeding, sale of animal parts, appropriate nuisance control methods, and use in scientific research. In some States, other legislative agencies dealing with domestic animals and veterinary practice may regulate use of wildlife contraceptives. The situation is further complicated by land ownership patterns. A recent report by the Southeast Deer Study Group (1993) indicated that 90 percent of the white-tailed deer habitat in the 16 member States is in private ownership. Thus at the State level, there is concern whether current regulations and authorities adequately define control over determining when, where, and how contraceptives may be used with wildlife populations. Most States would probably need new legislation to clarify issues pertaining to permitting, reporting, training and qualification of personnel, and protocols for administering contraceptives to specific wildlife species.

Uncertainty also exists concerning regulation of wildlife contraceptives by Federal agencies. The Subcommittee on Wildlife Contraception of the International Association of Fish and Wildlife Agencies reviewed regulatory authority over these drugs (Southeastern Cooperative Wildlife Disease Study Group 1993). The subcommittee reported that no registration of a wildlife contraceptive vaccine either as a pesticide (U.S. Environmental Protection Agency) or a vaccine (U.S. Department of Agriculture or U.S. Food and Drug Administration [FDA]) has been applied for or approved. Mallory (1993 unpubl.) stated that wildlife contraceptive vaccines are regulated by the Center for Veterinary Medicine at FDA. The Food, Drug and Cosmetic Act of 1938 (FDCA) requires FDA approval before marketing any drug not generally recognized as safe. A new animal drug is presumed unsafe with respect to any particular use or intended use unless an application pertaining to such use or intended use is approved by FDA. In general, approval of a new animal drug application by the FDA is a lengthy and expensive process.

Biological Issues

Health-related issues concerning use of wildlife contraceptives include effects on target and nontarget species and effects on humans who consume carcasses or have other contact with contraceptive materials. Nettles (1993 unpubl.) identified the following concerns about use of contraceptives in white-tailed deer; however, many of these concerns would apply to other species as well:

1. Will contraceptives cause females to experience an abnormal number of estrous cycles, expending stored energy and increasing predation on deer?

2. Will males expend themselves by repeatedly breeding sterile females that are constantly recycling?

3. What effects will contraceptives have on pregnant animals concerning abortion, fetal resorption, uterine infection, birthing difficulties, and lactation failure?

4. What effects will contraceptives have on prepubertal animals concerning permanent sterility and growth defects?

5. What effects will contraceptives have on sex characteristics such as antler cycles?

6. An antisperm membrane vaccine for deer is under study (White et al. 1993). Will vaccinated does exposed to deer sperm experience anaphylactic shock? Will orchitis, epididymitis, or anaphylaxis occur in males inadvertently injected with antisperm vaccine?

7. Will remote injection or implantation of contraceptives cause traumatic injury problems or infection?

McShea et al. (1994) report that immunocontraception of does has dramatic effects on mating season and activity budgets of white-tailed deer. In that study, 30 does were captured from a wild population and porcine zona pellucida was remotely administered by darts to 20 does during October 1992. The 30 does were exposed to 5 bucks from November 1992 through March 1993. Although control does mated in December, contracepted does exhibited estrus behavior through February. Whereas locomotion constituted 18 percent of the activity budget of control does, it constituted 32 percent of the activity budget of contracepted does and 39 percent of the activity budget of males.

Nettles (1993 unpubl.) reports that although wildlife contraceptives currently being evaluated for deer are delivered by injection or implant, the final goal is to have an oral vaccine. Such an oral vaccine would probably be genetically engineered and would use a live virus or bacteria as a carrier. But there are several potential hazards associated with this approach:

1. The carrier virus or bacteria could be pathogenic to the target or nontarget animals. This concern would include safety of vaccinated animals for human consumption.

2. The carrier organism could be highly transmissible from the initial vaccinate to secondary nonspecific animals. This situation could result in a reproductive disease that—once introduced—might be impossible to remove from a wild population.

3. In the carrier organism, a genetic reassortment or mutational change might occur that would increase virulence and/or transmissibility.

Other concerns have been expressed concerning impacts of contraceptives at the population level (Nettles 1993 unpubl.). The efficiency of immunocontraceptives is dependent upon an effective immune response in the target animal. When contraceptive vaccines are administered, the animals with the best immune systems will be the most susceptible to

Table 1. Reported harvest of white-tailed deer in Jasper County, SC (1974–94)

Year	Club areas reporting	Antlerless tags issued	Bucks harvested	Does harvested	Total harvested	Harvest rate (deer/mi^2)
1974	39	—	2,120	687	2,807	5.8
1980	67	—	1,669	915	2,584	5.3
1985	62	1,706	1,853	1,016	2,869	5.9
1988	82	2,468	2,228	1,800	4,028	8.3
1990	19	3,824	2,381	2,536	4,917	10.2
1993	79	4,029	2,239	2,837	5,096	10.5

sterilization while those with the poorest immune systems will be the most refractory. Thus, the deployment of contraceptive vaccines could shift the gene pool in favor of immunodeficient animals with resultant increased susceptibility to pathogenic organisms. Another concern is the capability of a contraceptive-treated population to respond to a natural disaster that would not be selective in regard to sterile *v.* fertile animals. Thus, a contraceptive-controlled population could theoretically be pushed to the brink of extinction directly or through creation of a genetic bottleneck.

Potential impacts are not limited to the target species. The reproduction of nontarget species that consume oral contraceptives placed for target species or that consume carcasses of target species through predation or scavenging could be affected. Populations of predators or scavengers that use the target species as a food source could be reduced. There is also concern over the safety for humans who use contraceptive-treated animals for food, particularly with implanted materials, or for people who have particular sensitivity to drugs, such as pregnant women with potential impacts on a developing human fetus.

Economic Issues

Although the effectiveness of experimental treatments with contraceptives of wild populations of feral horses looks promising (Kirkpatrick 1993, Kirkpatrick et al. 1990), two important questions must be examined before application to wild populations of ungulates is considered: (1) What proportion of the populations must be treated, and (2) How much will it cost? The management of white-tailed deer populations in Jasper County, SC, will be used to illustrate the relevance of these questions.

Jasper County is located within the Coastal Plain of South Carolina. Land use is predominantly agriculture and forestry. Deer densities are estimated to be as high as 1 deer/5 acres in some areas (Lewis Rogers, pers comm.), and deer-caused damage in this area has reportedly caused repeated crop failures.

Expenditures for recreational hunting contribute significantly to the local economy. The annual economic impact of hunting on private land in Jasper County during 1990–91 was estimated at $9 million (Richardson et al. 1992). The deer-hunting season in this area extends from August 15 to January 1 with no limit on antlered bucks. Antlerless deer may be taken by permit from October 1 to January 1. Harvest trends from 1974 through 1993 reflect efforts by the South Carolina Department of Natural Resources to curb increases in deer density (table 1). During this period, total reported harvest nearly doubled while doe harvest increased fourfold.

Several studies suggest that 35–40 percent of adult does must be removed annually to stabilize a deer population at levels substantially below (60–70 percent of) carrying capacity (McCullough 1979, Downing and Guynn 1983, Guynn 1985). Thus, it can be assumed that 35–40 percent of the adult does would have to be treated annually with contraceptives to achieve this same level of population regulation.

About 25 percent of the total doe harvest in Jasper County is fawns; thus, of the 2,837 does reported harvested in 1993 (table 1), about 2,128 were adults. The current level of harvest does not appear to be constraining populations within acceptable levels; obviously, treating less than 2,100 adult does with contraceptives every year would not alleviate crop depredation problems. Administering contraceptives with darts to this number of animals would be impractical. An oral delivery system would be needed.

The costs of administering a contraception program plus the forgone economic losses from reducing or eliminating a major recreational hunting opportunity would be substantial. Who would pay the costs—Federal agencies, the South Carolina Department of Natural Resources, the county, landowners, or the members of the local community? It is doubtful that any or all of these groups collectively would be able to pay for such a program. The overall impact of attempting wildlife contraception as an alternative to sport hunting for managing deer populations in Jasper County could easily exceed $10 million annually.

Ethical Issues

Species such as the white-tailed deer have evolved with complex behavioral mechanisms that keep populations and their individual members fit and competitive. The disruption of these mechanisms and the resulting population impacts imposed by sport hunting, contraception, or any other management practice should concern everyone. Preservation of the natural processes that define free-ranging populations of wildlife should concern everyone as well as the welfare and death of individuals. A large part of this dilemma can be attributed to the way in which people view the natural world.

In a video for the American Forest Council (1991), Gustare Repie discussed the forest archetype of American culture. An archetype is simply the way people think about any one certain idea or object in a given culture. As an illustration, he described the failure of marketing French cheese products in the United States. In France, cheese is displayed in the open without refrigeration. Customers can smell, feel, and taste the cheese, buying whatever amount they desire. Cheese is a living thing to the French. In contrast, Americans are accustomed to seeing cheese highly processed, wrapped in cellophane, and refrigerated. Cheese is dead. Marketing cheese in American stores in the typical French manner was offensive to Americans and sales of the product were a dismal failure.

Repie's forest archetype assumes three perceptions: the natural forest, the managed forest, and the jungle. The natural forest perception resembles the fantasy of Disneyland—there is no death, predation is bad, there are no humans, and the hand or influence of humans is unseen. Humans constitute a visible part of the managed forest with destruction, cutting of trees, and exploitation being the norm. Connotations include killing of the bison and removal of the Native Americans from their homelands, for example. In the jungle is the true natural forest—every living thing is subject to death, competition for basic resources is universal, and humanity is at best an abstract concept. Few Americans appreciate this perception, especially if humans are viewed as part of the jungle rather than separate from the jungle.

If they deliberately tamper with natural interactions, scientist-managers must be careful to consider all the impacts that any management approach may have on individual species of wildlife and the ecosystems in which they live. Consideration must be given to species populations and their function as well as the humane treatment of individuals. Those who utilize contraception methods must convey the limitations of contraception as well the positive attributes so that society does not view this tool as a cure-all for wildlife management problems.

Conclusion

Is wildlife contraception a reality or an illusion? I conclude that it's both. The technology exists to make wildlife contraception a reality for controlling populations of large ungulates on small confined areas such as zoological settings and islands. The potential in these situations to prevent environmental damage and provide esthetic benefits is great. As a generalized tool for managing species with high reproductive rates, such as the white-tailed deer, in unconfined free-ranging populations, contraception is currently an illusion. Even if the technology were currently in place, the legal, biological, economic, and ethical issues that must be considered will likely require decades for resolution.

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Human Dimensions of Contraception in Wildlife Management

Paul D. Curtis, Daniel J. Decker, Rebecca J. Stout, Milo E. Richmond, and Cynthia A. Loker

Introduction

Wildlife damage management was so much simpler in the good old days. If deer *(Odocoileus viginianus)*, beaver *(Castor canadensis)*, or other animals were a problem in a particular situation, people simply had them shot, trapped, or poisoned. Not many years ago, most people would go along with this approach, and those who didn't like it were marginalized as the "radical fringe." Not so today. Greater and more diverse segments of the public want a say in what professionals decide to do with *their* wildlife. The public wants to participate in setting objectives for management and in approving the methods for accomplishing those objectives. Kania and Conover (1991) emphasized that wildlife agencies should respond to these societal changes rather than resist them, thereby enhancing the value of the wildlife resource for *all* people. Changes in sociopolitical values have resulted in more stakeholder groups who want to be included in wildlife management decisions today than at any other time since the advent of applied wildlife management in North America (Curtis and Richmond 1992).

Although public attitudes and beliefs regarding wildlife have always been dynamic, public interest in wildlife and desire for input into management of wildlife have increased since the early 1970's. In response to this phenomenon, an area of social science inquiry and application to management has developed within the wildlife management profession—the human dimensions of wildlife management. Basically, human dimensions efforts focus on identifying what people think and do regarding wildlife, understanding why, and applying that understanding to the wildlife management decisionmaking process.

Some wildlife management professionals operating in the human dimensions arena have advocated the notion that we are now working within a new paradigm for management, one that strives to integrate the biological and human dimensions of wildlife management for improved decisionmaking and objective accomplishment (Decker et al. 1992). This represents a philosophical and pragmatic shift from an approach where biological science was the primary source of information for decisionmaking and the pervasive public sentiment of the time was in line with management professionals' values (Decker et al. 1991). However as a diversity of stakeholders emerged, wildlife managers were confronted with conflicting points of view. Under the new paradigm, social and biological information, as well as management experience, are part of the information base used in decisionmaking (Decker et al. 1992). This contemporary paradigm for wildlife management recognizes that decisionmaking occurs in an environment having sociocultural, economic, physical, legal, and administrative aspects, as well as biological components (Decker et al. 1992, Slate et al., 1992).

The new paradigm also includes consideration of the human dimensions when determining goals and objectives for management and in measuring outcomes of specific actions (Knuth and Nielsen 1989, Decker et al. 1992). In contemporary wildlife management, we recognize that many people representing a variety of views are legitimate stakeholders in management. Some of these people have no particular "use" for wildlife (i.e., food, recreation, or other utility). They may simply value wildlife for esthetic attributes or other nonconsumptive values. Thus, several different human values, beliefs, and attitudes (Kellert 1980) are playing an increasing role in establishment of wildlife management goals and objectives. Such human attributes are also playing greater roles in determining the social acceptability of management decisions and actions, including selecting and applying population control methods. In fact, Schmidt (1992) argues that natural resource management decisions, previously thought to be defined by science and economics, are driven by human values.

Knowledge concerning various stakeholders' reactions to conventional management approaches in nontraditional situations (i.e., wildlife management in urban and suburban environments) is imperfect. Recent, accumulating experiences indicate that these nontraditional wildlife management settings call for innovative approaches, including the development and application of new technologies. However, new technologies need to be developed and applied on a limited trial basis, with an eye toward anticipating and evaluating social acceptability. As new technologies are being considered, one needs to ask whether the innovation hoped for is consistent with the beliefs and values of affected stakeholders. Although minority opinions can be problematic to management programs, these viewpoints can provide important balance to a decisionmaking or planning process.

The purpose of this paper is to begin discussion of the human dimensions of contraception in wildlife management that developers of this emerging technology should consider as biological research proceeds. We draw limited inference from literature about human values toward wildlife, and human use and management of wildlife, to the use of contraception in management. We also identify issues that managers and other decisionmakers who formulate wildlife policy should consider as they contemplate applying contraception as a wildlife management tool. Because no studies have focused on identification and explanation of people's beliefs and attitudes about this new technology, we caution that this discussion is exploratory, not definitive. We also identify additional research needs in the area of human dimensions that could provide valuable insight concerning wildlife contraception issues.

Wildlife Management Stakeholders

Researchers who are developing wildlife contraception technologies need to understand the views that stakeholder groups hold concerning the application of new contraception methods and why differences exist. Beliefs and values that underlie various perspectives and the acceptability of wildlife contraception should be considered during research and development, before too much time and money are invested in approaches that may later prove to be morally or ethically unacceptable.

For example, Turner et al. (1992) noted that female white-tailed deer treated with a porcine zona pellucida (PZP) vaccine continued to cycle after not becoming pregnant. It is possible that PZP treatment could affect long-term patterns of deer behavior and social organization. Deer that expend extra energy for breeding activities may not survive a harsh winter.

Moen (1976) noted that seasonal physiological changes occur, and deer conserve energy in winter by reducing their general level of activity. Consequently, deer should remain as undisturbed as possible during winter, and increasing the length of the breeding season will likely have serious impacts on seasonal changes in deer physiology.

These changes in deer reproductive biology raise serious ethical and management questions, and they may influence stakeholders' perceptions of this contraceptive technique. Stakeholders must understand the full range of effects that different contraceptive methods may have on deer populations before making decisions to accept or reject their use. Also, sensitivity to key stakeholders' values and beliefs during the development stages, prior to widespread field applications, are extremely important. The wildlife profession may spend millions of dollars developing and registering new contraceptive technologies yet still face public controversy if the interests and concerns of all stakeholder groups are not carefully considered and addressed in advance of implementation.

Who are key stakeholders in the wildlife contraception arena, and what can managers conjecture about stakeholders' opinions on contraceptive applications? Identification of stakeholders is an essential human dimensions component when considering various management options. Key stakeholders would be similar in population management situations whether wildlife contraception or other direct management methods (i.e., shooting, trapping, etc.) are being considered or used. The claims made by stakeholders may seem different, but the fundamental values that lead to their expressed views likely will be consistent with those observed in past studies unless contraception technology taps into different values and beliefs. Stakeholders include wildlife management professionals, researchers developing the technology, industry representatives hoping to produce and market the technology, potential regulating agencies (e.g., the Department of Health and Human Services' Food and Drug Administration, the Environmental Protection Agency, State health departments, etc.), Federal and State land-management agencies, wildlife damage/nuisance control operators, people experiencing damage or wildlife-related health and safety risks, extension wildlife specialists, people concerned about animal welfare, animal rights advocates, elected public officials, hunters concerned about a competing management tool, environmentalists, taxpayers concerned about costs, media representatives, and religious leaders in communities. Depending upon the site-specific situation, this list of stakeholders could be expanded or condensed.

Anticipating Issues Regarding Contraception Technology

Animal Rights and Animal Welfare Concerns

Schmidt (1990) proposed a distinction between animal rights and animal welfare advocates that has great bearing on how we think different stakeholders will view wildlife contraception. Animal rightists fundamentally believe that animals should be extended rights similar to humans, because to do otherwise would constitute speciesism (Singer 1980). This belief differs from that of animal welfare supporters, who focus primarily on the humane treatment of animals, though these people may not believe that animals and humans have equal rights. Although most of the animal rights confrontations with wildlife management have focused on hunting and trapping, there are few indications that animal rights advocates would find contraceptive use in wildlife management much more acceptable philosophically. We speculate that denying animals the right to procreation, giving them no "say" in the decision, or manipulating individual animals to further human needs, seems to be as great a violation of the animals' rights (thinking of the human analogy) as taking their lives through hunting. Thus, we forecast no significant improvement in relations between wildlife managers and animal rights advocates because of contraception technology.

Animal welfare advocates will likely favor contraceptive technology if pain and stress to wildlife, unnecessary animal deaths, or other concerns about humane treatment of animals are minimized. Some momentary stress or pain will be acceptable if, on balance, contracepting wildlife will reduce mortality of animals by starvation, disease, motor vehicle accidents, selective culling, or other factors. However, opposition may mount if contraceptive materials affect animal breeding biology (e.g., late-born fawns, extending the buck rut into midwinter, etc.) or other behaviors that raise serious welfare concerns.

As something of an aside, we do see a new dynamic occurring relative to animal rights advocates and contraceptive technology issues. Unlike most battles between animal rightists and wildlife management advocates, where hunters bear the brunt of public scrutiny, it is likely that hunters may be spectators in many situations where contraception is being considered for application, especially in residential or park landscapes where hunting is less feasible. Values and beliefs of many suburban property owners (i.e., homeowners, motorists, gardeners, etc.) who desire relief from nuisance wildlife and are concerned about wildlife-related health and safety risks to people (e.g., Lyme disease, rabies, deer–vehicle collisions, etc.) will be opposed by groups who espouse the animal rights philosophy. Animal rights advocates may find themselves battling those people who previously have been part of the silent majority concerning wildlife management issues, rather than focusing on hunters and trappers.

Contraception v. Hunting

As the development of contraceptive methods moves forward, we anticipate wildlife contraception will affect public perceptions of the necessity for hunting. For perhaps 50 years, the wildlife profession has told hunters and the public at large that hunting is the most cost-effective tool for management of overabundant wildlife populations. That statement has become a standard defense for the justification of regulated hunting. Of course, hunting is the primary method used for managing a few wildlife species (e.g., deer and elk *[Cervus elaphus]);* however, it has not been proven that regulated harvests can effectively control other wildlife populations. So what are the consequences for hunting if an effective wildlife contraception method is developed and society is willing to pay for its application? Will wildlife contraception signal the demise of hunting?

The future of hunting was recently discussed at the North American Hunting Heritage Symposium. Decker et al. (1993) asserted that the future of hunting lies in public understanding and acceptance of the sociocultural values related to hunting, not for its value as a form of recreation or a tool for wildlife population management. Thus, some researchers believe that whether or not contraception technology evolves to become economically feasible, the future of hunting is dependent upon other factors, such as maintaining a rural cultural tradition.

Contraception v. Other Direct Lethal Methods

Direct (e.g., shooting, kill-trapping, poisoning, etc.) and indirect (e.g., induced abortion, etc.) methods for lethal management of wildlife populations have been applied or tested experimentally in the past. Public acceptability of these lethal methods depends on the species of wildlife in question and perceived human health and safety risks. Based on a survey of homeowners (*n* = 391) with nuisance wildlife problems (Braband and Clark 1992), most respondents approved of lethal control for rats and mice (Cricetidae, 95 percent), moles (Talpidae, 79 percent), snakes (Serpentes, 74 percent), bats (Chiroptera, 71 percent), pigeons *(Columba livia,* 60 percent) and skunks *(Mephitis* spp., 57 percent). However, most people disapproved of lethal control for deer (70 percent), geese *(Branta canadensis,* 67 percent), woodpeckers (Picidae, 65 percent), and squirrels (Sciuridae, 59 percent). For many respondents, humaneness was equated with nonlethal control, and nearly 90 percent indicated that humane treatment of nuisance animals was important.

It seems certain that nonlethal methods would be preferred over direct lethal methods by animal welfare and other similar stakeholder groups if the nonlethal approaches are equally effective and carry similar costs. It is also likely that lethal methods which have added benefits would be preferred over lethal methods that have no added value (e.g., recreational hunting would be preferred over poisoning). This idea of relative acceptability has not been adequately investigated and deserves future inquiry. Increasing professionals' understanding of public acceptability of various lethal and nonlethal methods would be useful in management decisionmaking and in developing research agendas to meet future wildlife management needs of society. The findings of such a line of inquiry might also be useful for creating educational programs concerning tradeoffs about which approaches to take in various situations.

So far in this discussion, we have treated wildlife contraception as a nonlethal management technique. Yet even this assumption may be questioned by some stakeholders in wildlife management decisions. This is both a value-based (Decker et al. 1991) and biologically based judgment. Prevention of conception may be equated with the "unnatural" death or management of an animal by some segments of society. Even when groups of animals such as deer are trapped and transported to another location, some mortality typically occurs during transport. Defining what are lethal *v.* nonlethal techniques may not be as obvious as initially expected. Such thoughts call for additional public retrospection about the value of "wild" in wildlife populations.

Contraception v. Nonmanagement

A segment of society supports the nonmanagement viewpoint. That is, some people believe that humans should simply "leave nature alone" and "learn to live with wildlife." This perspective does not fully recognize the immutable impacts that humans have had, and will continue to have, on the environment for centuries to come. Certainly, the "leave it alone" perspective is attractive because proponents believe that wildlife populations will take care of themselves; however, the consequences of wildlife extinction or overpopulation may damage both ecosystems and people. Regardless, wildlife contraception would likely be unacceptable to many nonmanagement advocates, as would any other wildlife management tool. Any purposeful intervention by people to manipulate wildlife could be viewed as altering the "naturalness" or "wildness" of animal populations. However, faced with animal overabundance and deterioration of habitat quality, research and management professionals from some areas (e.g., national parks and wildlife refuges, State parks, etc.) that have typically been managed under a natural-systems approach are actively exploring the development and application of contraceptive technologies to control large ungulates (Kirkpatrick et al. 1990, Turner et al. 1992).

Public Beliefs and Values About Wildlife and Wildlife Management Via Contraception

Our literature review uncovered no research concerning public attitudes toward contraception in wildlife. Position papers and other nontechnical writings abound, but we were unable to find a single comprehensive study describing the nature and basis for public attitudes toward either wildlife or human contraception. Similarly, we were unable to find studies of people's attitudes about contraception in companion animals. Thus, we draw entirely on research about human attitudes toward wildlife and various uses of animals when discussing attitudes and beliefs that likely will be pertinent in assessing the degree of public acceptability for contraception in wildlife.

It's important to remember that people's beliefs and attitudes about wildlife are formed, exist, and change in a context of broader attitudes and values concerning several domains of their lives. For example, people's broader world view concerning what constitutes appropriate human interaction with the environment or nature has profound effects on how people view human–wildlife interactions. Wildlife-associated attitudes and values are also related to other major world views, such as religious beliefs, beliefs about safety and security (both physical and financial) of family and community, and beliefs about individual freedom of choice in dealing with problems (i.e., those caused by wildlife).

Studies by the Human Dimensions Research Unit in the Department of Natural Resources at Cornell University have examined the wildlife-related attitudes and values of thousands of people on a variety of subjects during the last 15 years. Based on these studies, a Wildlife Attitudes and Values Scale (Purdy and Decker 1989) was developed and applied in over a dozen studies. Essentially, this work identified the existence of three broad dimensions of public attitudes toward wildlife: wildlife use, wildlife preservation, and wildlife damage/nuisance tolerance.

The wildlife-use category includes a traditional wildlife conservation philosophy that supports use of wildlife for human benefits and management to accomplish such purposes. Attitudes and values associated with hunting, trapping, and similar activities would be reflected in this dimension.

The wildlife-preservation category embodies concerns for individual animals and for their continued existence in nature. Animal rights notions would be on the extreme end of this set of attitudes and values.

The wildlife-problem-tolerance set of attitudes and beliefs is interesting conceptually because they discern that people have a wide range of acceptability of various human–wildlife interactions. Other research and observation lends credence to the existence of thresholds of tolerance for wildlife-caused problems depending upon economic or health and safety risks. For example, some people will incur a high level of economic damage from wildlife before they find the tradeoff tips toward wanting relief. Damage tolerance has been documented for both farmers (Decker and Brown 1982, Decker et al. 1984) and homeowners (Sayre et al. 1992). However, when the perceived risk of health and safety problems associated with wildlife (e.g., rabies, Lyme disease, motor vehicle accidents, etc.) reaches even modest levels, tolerance of wildlife presenting the risks is reduced markedly (Connelly et al. 1987, Stout et al. 1993). A recent survey of Tompkins County, NY, residents indicated the perceived risk of being involved in a deer–vehicle accident, along with attitudes toward deer and the degree of personal involvement with deer–vehicle collisions, predicted the likelihood that a person would support reducing the local deer population (Stout et al. 1993). Results from this New York experiment suggest that people change their attitudinal orientation if perceived risks of economic loss or health and safety impacts exceed certain thresholds of tolerance (which need further assessment for precise estimation).

To learn more about public attitudes toward a variety of deer-management alternatives in a suburban environment, we conducted a survey of property owners in the greater Rochester, NY, metropolitan area. The paucity of scientifically obtained information documenting people's beliefs about contraception in wildlife management, and lack of management experience in this new arena, encouraged us to explore these issues. The survey instrument included several questions concerning contraceptive management of a locally overabundant deer herd. Public attitudes and values related to the acceptability of contraception as a deer management technique are discussed further below.

Identifying Public Acceptance of Contraception: A Pilot Study

Wildlife managers considering the use of contraception for resolving wildlife problems need knowledge of the specific attitudes held by stakeholders in a given management situation. The greater Rochester area was selected as the site for a pilot study because of a long-standing deer-management controversy surrounding Durand Eastman Park and implementation of a public involvement process for setting deer management objectives (Curtis et al. 1993).

To determine the attitudes of suburban residents toward deer management, a questionnaire was sent to 1,590 residents living in the Rochester area during 1992. Questions were developed with input from New York State Department of Environmental Conservation (DEC) staff. The primary objectives of the survey were to assess public attitudes about deer, perceptions about deer-management methods, and the public acceptability of various management options, including contraception.

Approximately 750 residents completed the questionnaire (a 47-percent response rate). A followup phone survey of people who did not respond to the questionnaire indicated that many people were either not interested in deer-management issues or had difficulty understanding the questions and concepts. The majority of respondents selected either contraceptive methods, managed hunting, or trapping and releasing deer to the wild as their preferred deer-management option.

People who supported contraception were more interested in minimizing the suffering of deer than respondents who did not support contraception. Respondents who thought deer contraception was an extremely acceptable management option were also more likely to be dissatisfied with DEC's deer-management program and tended to agree with the statement that "herd size should be guided by nature alone."

Important considerations of those opposed to contraception included maximizing hunting opportunity and minimizing economic costs to society. In addition, people who were satisfied with DEC's deer-management approach were more likely to view contraception as unacceptable.

The credibility of 21 potential sources of deer-management information was associated with the acceptability of deer contraception as a preferred management option. People who selected contraception as their preferred option tended to rate the Humane Society of Rochester, Save Our Deer, and Helmer Nature Center with greater credibility than respondents who preferred other deer-management methods. Conversely, those who did not select contraception ranked the local hunting club and the Irondequoit Deer Action Committee with greater credibility. However, DEC ranked as the single most believable source for deer information among both supporters and opponents of deer contraception.

It is not surprising that respondents who were interested in maximizing deer-hunting opportunities and reducing economic costs were generally opposed to contraception. Because hunting is the primary method used by DEC to manage deer in New York, respondents who were satisfied with DEC's deer-management program were also more likely to view contraception as an unacceptable alternative. However, it's important to note that about 50 percent of respondents selected either minimizing human health and safety risks or maintaining a healthy deer population as the most important deer-management consideration, regardless of whether respondents supported or opposed contraception.

Research Needs for Human Dimensions of Wildlife Contraception

This pilot investigation of citizens' attitudes toward deer contraception can contribute to a broader understanding of public beliefs about contraception in wildlife. In similar situations, it's important to identify relevant stakeholder groups along with their size, position on the issue, salience of the issue to them, perceived stake in the issue, power in decisionmaking (political influence), knowledge of the issue, and socioeconomic and demographic characteristics. Inquiry must go beyond description because wildlife managers and policymakers need to know why people hold various beliefs and attitudes and if these attitudes are based on accurate perceptions of wildlife ecology and contraceptive techniques. That information will help professionals identify the extent and nature of educational communications need. Also, it's useful to know how rigid or malleable attitudes are. Obviously, educational programs can influence change only if the public's attitudes are flexible.

One limitation of our pilot study is that we painted contraception for deer management with a very broad brush and did not define specific technologies or delivery systems. For example, delivering contraceptive vaccines via oral baits, dart guns, "bio-bullets," or arthropod vectors may have characteristics that tap into different underlying values held by various stakeholder groups. Also, specific technologies (i.e., using genetically recombinant proteins or genetically altered viruses, etc.) for developing vaccines for reproductive inhibition may be unacceptable to some publics. Mammalian reproductive biology is similar across species, and the chance of mutations in genetically altered viruses may pose substantial risk. Consequently, when examining attitudes and beliefs of people toward contraception in wildlife management, it will be extremely important to identify both the specific material and delivery system that will be used and to be certain that stakeholders understand how they work.

Public Involvement Strategies for Making Management Decisions

In addition to human dimensions research, increasingly the wildlife management profession is finding that public-involvement techniques are helpful in reaching community consensus on controversial wildlife management issues (McMullin and Nielsen 1991, McAninch and Parker 1991, Nelson 1992, Curtis et al. 1993, Stout et al. 1993). Conceived carefully and implemented effectively, citizen participation strategies present educational opportunities, improve agency image as being responsive to stakeholder needs, and lead to more acceptable, if not universally embraced, decisions and actions to solve management problems (Stout et al. 1993). Different public-involvement models have been used in Minnesota (McAninch and Parker 1991) and New York (Curtis et al. 1993), and these can be assessed for suitability and adapted to fit other situations. In New York, the work of citizen task forces was greatly enhanced by the availability of systematically collected human-dimensions data gathered from the community at large or from members of specific stakeholder groups. Results from systematic, ongoing evaluations of citizen participation activities can be used to feed into and improve the process as it is being carried out and are invaluable for effectively managing the process (Stout et al. 1992).

Human dimensions studies and citizen participation strategies take time and money, but there is no indication that these costs are any larger than those incurred when such strategies are not included in the development of management policy. The difference is that proactive efforts are more predictable and manageable than the time and cost of reacting to problems after an unacceptable decision is made and the management agency has to resort to the typical "damage control" mode of operation.

A special group of stakeholders should be the focus of immediate inquiry—wildlife management professionals. Whether it's wildlife contraception or any other innovation or deviation from traditional approaches to wildlife management, members of the profession are extremely important stakeholders. These professionals have the credibility to scuttle innovation or to accelerate its adoption. Some members also have loyalties to the conventions of the profession, and basic beliefs and values are fundamentally difficult to alter (Sanborn et al. 1994). We believe that the advent of contraception in wildlife management may signal a significant change in the way wildlife managers do business. If that prediction is on track, then it is clear that resistance to contraceptive technology will emerge. Thus, we believe it is important to understand the attitudes of members of the wildlife management profession on this topic. Publications such as this facilitate discussion, reveal positions, etc.; however, we also need empirical analyses to help the profession grapple with contraception in wildlife management and related issues looming on the horizon.

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Thunder in the Distance: The Emerging Policy Debate Over Wildlife Contraception

R. Bruce Gill and Michael W. Miller

Abstract: Wildlife contraception is only now emerging as a wildlife policy issue. It will emerge into a sociopolitical environment that is already polarized from a clash of ideologies. The wildlife conservation/hunting community strives to preserve the status quo while animal welfare and animal rights activists struggle to change wildlife management philosophy and practice to conform to their respective beliefs. Recent professional and popular literature reveal at least four major areas of conflict: (1) antimangement sentiment, (2) antihunting sentiment, (3) animal rights sentiment, and (4) animal welfare sentiment. Wildlife managers anticipate that the conflict over the use of contraceptives will involve value and belief conflicts between traditional wildlife management and animal rights proponents. We believe instead that the primary conflicts will revolve around pragmatic issues such as when, where, and in which circumstances managers will use the contraceptive tool. In this context, wildlife contraception will be regarded as a "mixed bag." Given the nature and potential polarity of the wildlife contraception issue, wildlife agencies will have to behave proactively by projecting themselves into their future. Currently, wildlife agencies respond to many policy challenges reactively and defensively in an attempt to preserve their past. If a productive compromise can be reached over the issue of if, how, when, and where to use wildlife contraception, the wildlife policy decision process must be visionary, wise, bold, accessible, adaptable, and, most of all, fair.

Keywords: wildlife contraception, antimanagment, antihunting, animal rights, animal welfare, wildlife policy decision process

Introduction

> No policy that does not rest upon philosophical public opinion can be maintained.
> —Abraham Lincoln

History is a thread. It weaves from the past through the present and, inevitably, binds to the future. Earlier in this decade, wildlife policymakers in Colorado experienced an historical precedent event. On November 3, 1992, voters successfully overturned Colorado Wildlife Commission policy and outlawed the practices of hunting black bears in the spring and hunting them with bait and dogs (Loker and Decker 1995). This was the first time in Colorado history where wildlife policy was established by a citizen-referred ballot initiative. That historic event will ineluctably bind the State's past to the future because it marked a monumental failure in the policy decision process and strained State officials' credibility to deal with future controversial wildlife management issues.

In the black bear management controversy, agency officials failed to *see* when they looked. They failed to *listen* when they heard, and they failed to *act* while there was time. They did not see a subtle evolution of public wildlife values. They did not listen to the growing chorus of public discontent. They did not act while the management environment was still tractable. We believe this failure resulted because wildlife policymakers in Colorado were unaware of or insensitive to the social *context* into which the bear hunting issue intruded. This, in turn, allowed the issue to evolve into a polarized *controversy* before policymakers attempted to forge effective *compromises.* Furthermore, we believe the wildlife contraception issue has similar characteristics to follow a parallel evolutionary path unless policymakers assume a proactive posture from the outset.

Context

Wildlife contraception is only now emerging as a practical tool to control growth of wildlife populations (Kirkpatrick and Turner 1991, Garrott et al. 1992). Expectations have been raised which already seem to exceed the likely potential of the technology. Indeed, its emergence is being hailed by some as the "magic bullet" to solve the problem of controlling wildlife populations where hunting is not a viable option (Kirkpatrick and Turner 1991). Nontheless, this genesis promises to be anything but tranquil.

First, wildlife policymakers will be unable to control either the development of animal contraceptive technology or its availability. Pharmaceutical companies currently project two major markets for animal

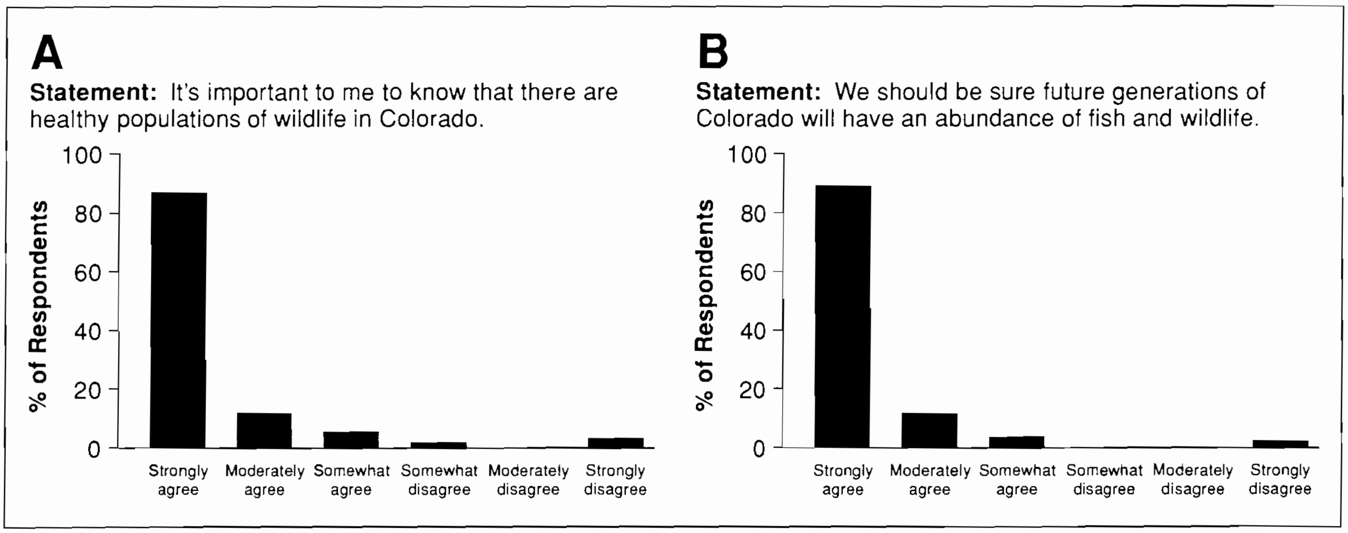

Figure 1. Indexes to the value Coloradans place on their wildlife: (A) Existence value, (B) Preservation value.

contraceptives, animal production and pet neutering. They also project it will be a multimillion to multibillion dollar industry. For example, one estimate suggests that between 5.7 and 12.1 million dogs and cats are euthanized each year in America due to pet overpopulation (Olson et al. 1986). Contraception is regarded both as a more humane and a more economical solution to pet overpopulation than euthanization or surgical sterilization (Maggitti 1993). Consequently, animal contraception will be available as an alternative to lethal wildlife population control irrespective of the desires of wildlife agency policymakers.

Second, environmental values have been metamorphosing throughout the world for several decades. Whereas *laissez faire* attitudes predominated in the last century, twentieth century values have grown increasingly "green" (O'Riordan 1971, Dunlap 1991, Kellert 1993, McAllister and Studlar 1993). Contemporary environmentalism, with its emphasis on environmental protection, now enjoys widespread public support (Sagoff 1990). Wildlife agencies, on the other hand, increasingly find themselves stuck in the backwater of a bygone era of maximum sustainable use. Public support for wildlife policies based upon wildlife uses seems to be waning. As a result, support for agency wildlife management policies has weakened as opposition has intensified.

Contemporary Public Attitudes

Colorado has long been regarded as a political bellwether State because of its geographically and philosophically diverse population. If so, perhaps the situation in Colorado forecasts trends in public wildlife values as well. The Colorado Division of Wildlife has been conducting public opinion and attitude surveys concerning wildlife issues at least since 1986. When we review the context of public attitudes, we see both consensus and conflict. We have consensus that wildlife is highly valued and conflict over how it should be valued. Consider the statement: *"It's important to know that there are healthy populations of wildlife in Colorado."* Virtually everyone concurs (fig. 1A). Similarly, when we ask if wildlife preservation should be a priority wildlife agenda item, affirmation is equally strong (fig. 1B).

Consensus dissolves, however, when we infer purpose from value. Colorado statutes declare it State policy to manage wildlife for *"the use, benefit, and enjoyment of people."* Although most would agree with managing for benefits and enjoyment, public values begin to diverge over the issue of use. Some say wildlife should be managed for consumptive uses, others say it should be managed for nonconsumptive enjoyment, while still others say we should manage people for the benefit of wildlife. Recent professional and popular wildlife literature reveals at least four major areas of conflict: (1) antimanagement sentiment, (2) antihunting sentiment, (3) animal rights sentiment, and (4) animal welfare sentiment (Goodrich 1979, Decker and Brown 1987, Schmidt 1989, Richards and Krannich 1991).

Antimanagement Sentiment.—Among Coloradans, public sentiment is divided over whether hunting is one of the worthy purposes of wildlife management. Surveys suggest that wildlife professionals and hunting advocates have overrated public sentiment against management. For example, a recent planning survey conducted for the Division of Wildlife by the Human Dimensions in Natural Resources Unit of Colorado State University asked Coloradans to express their agreement or disagreement with the statement: *"It is important for humans to manage populations of wild animals."* More than three-fourths of the respondents agreed that wildlife management is important (fig. 2A).

However, approval of wildlife management is conditioned by perceptions of management intent. When management is directed toward animal benefits,

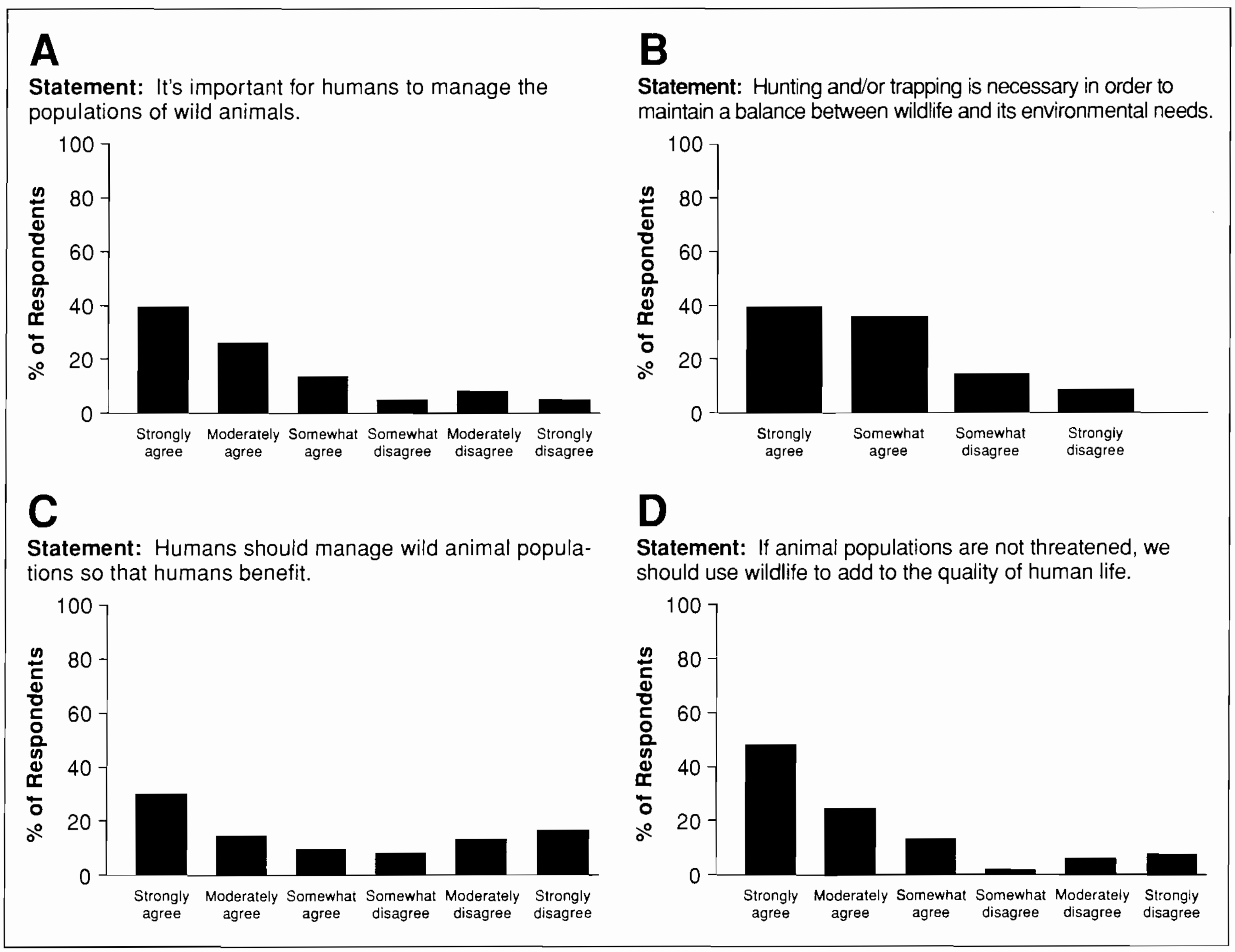

Figure 2. Indexes to antimanagement sentiment among Coloradans: (A) Support for wildlife management, (B) Support for hunting and/or trapping, (C) Support for managing wildlife for human benefits, and (D) Support for human use of wildlife to enhance the quality of life.

approval is strong. In a 1986 survey, nearly 75 percent of the respondents agreed that *"Hunting and/or trapping are necessary in order to maintain a balance between the number of wildlife and its environmental needs"* (fig. 2B). On the other hand, only 50 percent of Coloradans agree that *"Humans should manage wild animal populations so that humans benefit"* (fig. 2C). But as human benefits are clarified and conditioned—as in the statement *"If animal populations are not threatened, we should use wildlife to add to the quality of human life,"*—again, implicit support for wildlife management is high (fig. 2D).

It would seem that antimanagement sentiment per se is an unimportant public wildlife issue. Rather, the issue of management focuses on management outcomes. Management aimed at protecting wildlife populations from detrimental effects of their own excesses and focused on wildlife uses which enhance the quality of our lives is strongly sanctioned. Support declines, however, as the perceived nobility of purpose declines.

Antihunting Sentiment.—In general, the public does not appear to be prescriptively antihunting. When directly asked if wildlife agencies should disallow hunting, time and again the public responds that they should not. Even in the hotly contested black bear management controversy, antihunting sentiment was not a major factor affecting the outcome. For example, when a sample of prospective voters were asked to respond to the statement, *"As I read the following four statements about hunting please tell me which one comes closest to your views: A. Don't allow any hunting; B. Allow hunting only by wildlife professionals to control animal overpopulations; C. Allow hunting by licensed sportsmen; and D. Disallow hunting only when necessary to protect wildlife populations because hunting is a basic right,"* only 7 percent of Colorado's voting population supported the abolition of all hunting. Nearly 80 percent supported legal sport hunting so long as wildlife populations were protected from overharvest (fig. 3A).

Again, however, public support for hunting is conditional. Steve Kellert's earlier survey (Kellert 1980) and our more recent one found strong public support for meat hunting, less for recreational hunting, and little support for trophy hunting (fig. 3B). As was the case for management, the public seems to be saying, "We support hunting if it serves worthwhile social purposes, such as providing food for one's family." But when hunting deviates from the norm of public worthiness, it loses support.

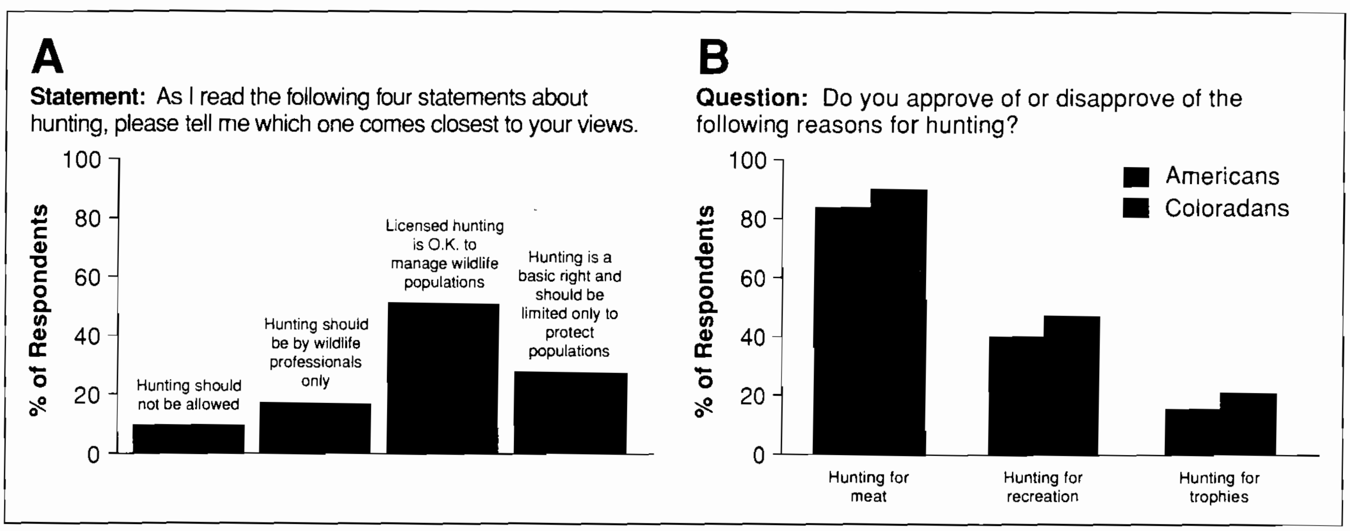

Figure 3. Indexes to antihunting sentiment among Coloradans: (A) Support for hunting, (B) Approval of reasons for hunting.

Table 1. Comparison of animal welfare and animal rights organizations (after Macauley 1987a–c)

Attribute	Animal welfare organizations	Animal rights organizations
Philosophies	Legalistic	Moralistic and legalistic
	Humanistic, benevolent	Libertarian, vegetarian, revisionist
	Reduce cruelty, unnecessary pain and suffering.	Eliminate suffering; elevate moral standing.
Concerns	Companion animals and endandangered species, whales, seals, some experiments	Factory farming and experimental animals
	Public abuses	Private as well as public abuses
	Individual abuses and species preservation	Institutional exploitation
Motivations	Emotional, ecological	Just, ethical
	Sympathy, kindness to animals	Philosophical
Strategies	Moderate	Radical or militant
	Regulationist, incremental	Abolitionist, revolutionary
	Educational, informational, preventative	Political, legal, reconstructive
Organizations	Comparatively large, established, national	Comparatively small, emergent, local or regional
	Well-endowed, hierarchical	Poorly funded, relatively decentralized
	Homogenous, wealthy, professional membership	Heterogenous, less affluent, diversely employed membership

Animal Rights Sentiment.—Wildlife professionals and hunting advocates infer cause and effect between animal rights sentiment and antihunting activism (Goodrich 1979, Richards and Krannich 1991). Despite this opinion, few public attitude surveys have investigated this connection. Much of the rhetoric and reaction to animal rights fail to separate public attitudes about animal rights from sentiments for animal welfare. Macauley (1987a–c, 1988a and b) conducted an intensive study contrasting animal welfare organizations with animal rights organizations. In general, animal welfare organizations oppose *unnecessary* pain and suffering among animals, including wildlife, whereas animal rights groups are generally opposed to human intervention in the lives of animals. Macauley concluded that animal welfare advocates are better organized, better funded, and more politically adept than animal rights groups. Strategies of animal welfare groups to change American values toward animals tend to be moderate, long-term, and educational in contrast to those of animal rights activists, which tend to be radical, immediate, and sensational (table 1). Regan and Francione (1992) characterize the philosophy of animal welfare advocates as "gentle usage" and contrast it with an animal rights philosophy which calls for "nothing less than the **total** liberation of nonhuman animals from human tyranny." We believe that general public values are more attuned to animal welfare than to animal rights philosophy.

We tried to tease these issues apart by examining responses of Coloradans to a variety of questions about animal rights and animal welfare issues. Animal rights sentiment was indexed by the statement: *"Animals should have rights similar to humans."* Astonishingly, perhaps, 60 percent of the respondents agreed, and one-third of these agreed strongly (fig.4A). What does this mean in terms of public attitudes to wildlife uses? In response to the statement, *"The rights of wildlife are more important than human use of wildlife,"* more than half of the respondents agreed, and of these, one-third strongly agreed (fig. 4B).

Nevertheless, when asked to make choices between rights and uses, once again the public discriminates. In response to the statement, *"I object to hunting because it violates the rights of an individual animal to exist,"* nearly two-thirds of the respondents disagreed, and one-third of these disagreed strongly (fig. 4C).

Animal Welfare Sentiment.—It would seem that Coloradans agree with the general notion that animals should have rights, but these rights should protect them from abusive uses, not all uses. Indeed, much of the conflict between animal uses and animal rights seems to center on the issue of animal welfare, and on this issue the public is much less equivocal. For example, the statement, *"I see nothing wrong with using steel-jawed leghold traps to capture wildlife,"* evokes strong opposition from most of the public (fig. 5A). What about perceptions of the humaneness of hunting? Here the public is divided. About one-half agree and one-half disagree with the statement, *"Hunting is cruel and inhumane to animals"* (fig 5B). In effect, the public seems to be saying, "No matter how important the management outcome, the end does not justify the means."

Controversies

So far, Statewide policymakers have treated public attitude responses as though the public was monolithic. This is clearly not the case. Wildlife values of Coloradans tend to cluster into four distinct types. Nearly one-third share the attitude that people can use wildlife to their benefit if wildlife populations are not endangered. Additionally, this sector believes that wildlife has the right to protection from abusive uses. Another cluster of similar size places high emphasis on commodity and recreational values of wildlife. A third cluster, representing about 25 percent of the population, strongly believes wild animals ought to have rights protecting them from human exploitation. A fourth cluster, representing less than 10 percent of the population, supports the use of wildlife for human benefits, such as food, fur, and fiber, but seems to be ambivalent toward recreational uses of wildlife. These

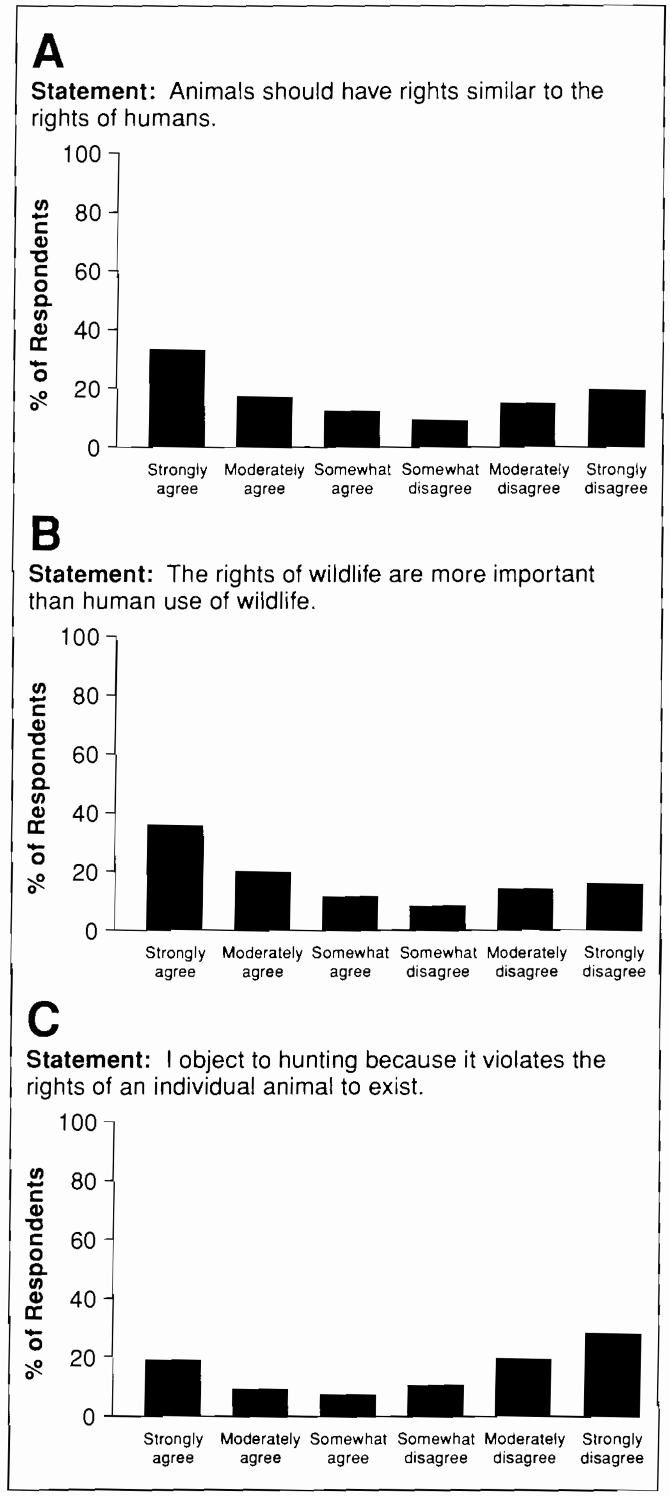

Figure 4. Indexes to animal rights sentiment among Coloradans: (A) Support for the concept that animals have rights similar to those of humans, (B) Support for the concept that animal rights supersede human uses of animals, and (C) Support for the concept that hunting violates the rights of animals.

people strongly oppose the concept that animals have rights (fig. 6A).

Given this fabric of social context, how are these contrasting publics likely to respond to the issue of wildlife contraception? We predict the following controversies will emerge. Those who strongly support hunting and animal uses will see wildlife contraception as a threat to hunting and will oppose its use vigorously. The animal rights community will be divided on the issue of wildlife contraception. Some will see it as a much preferred alternative to hunting because it is nonlethal and will insist it replace hunting as a wildlife population control tool. Others in this cluster will see wildlife contraception as just another interventive tool for humans to dominate animals. Those who moderately support animal rights and uses will support wildlife contraception to manage nuisance wildlife and will judge its utility to other management issues on a case-by-case basis. Those who are moderate toward animal uses, low on support for hunting, but strongly against animal rights will have mixed responses. Some will support wildlife contraception if it is more effective than hunting or trapping to control wildlife populations. However, most will

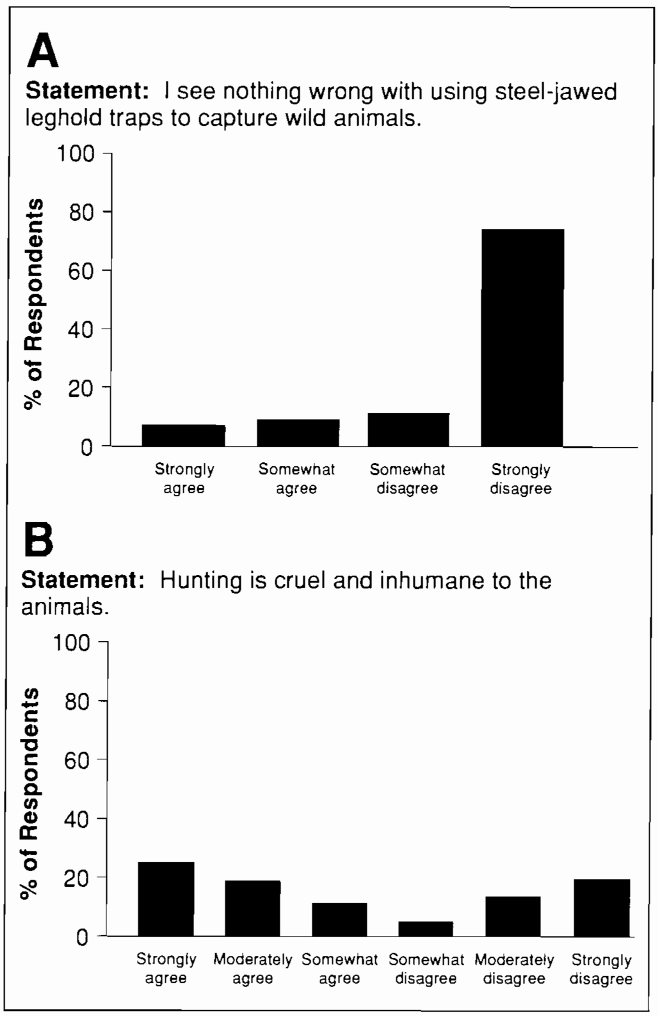

Figure 5. Indexes to animal welfare sentiment among Coloradans: (A) Opposition to the use of the steel-jawed trap, and (B) Support for the concept that hunting is cruel and inhumane to animals.

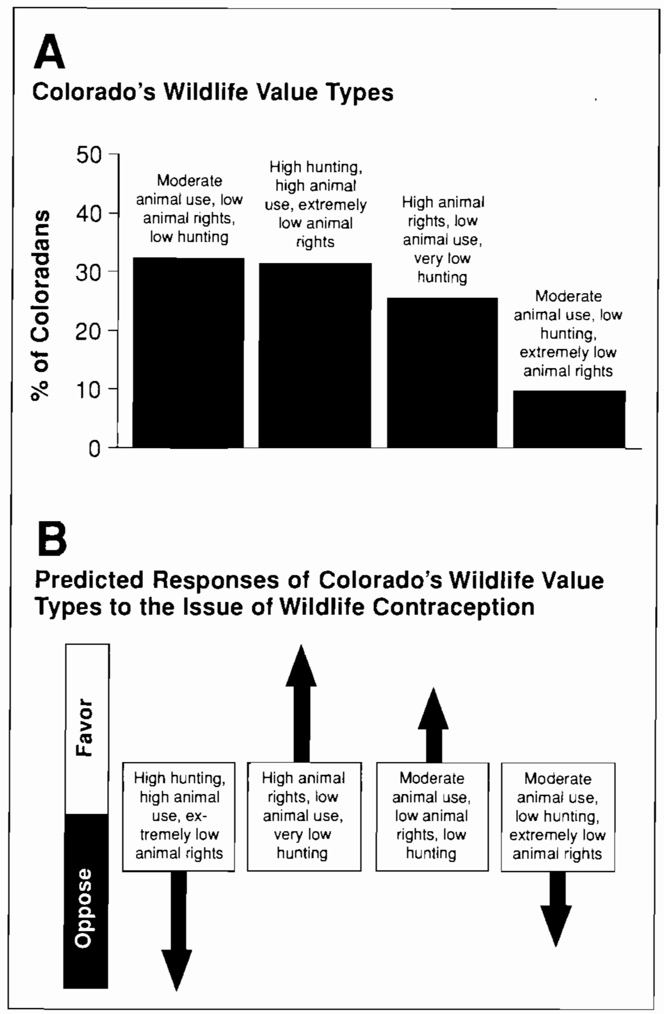

Figure 6. (A) Clusters of wildlife value types in Coloradans, and (B) Predicated responses of Colorado's wildlife value types to the issue of wildlife contraception.

Table 2. Advantages and disadvantages of competing wildlife contraception technologies

Contraceptive technology	Advantages	Disadvantages
Steroidal contraceptives	Readily available	Remains in the food chain
	Orally active	Lengthy Food and Drug Administration approval
	Reversible	Slow biodegradation
Immunocontraceptives	Reversible	Requires multiple treatments
	Inexpensive	Currently not completely efficacious
	Amenable to remote delivery	Must be developed specifically for each species
	Minimal side effects	
	Rapid biodegradation	
Hormonal toxin contraceptives	Requires only a single treatment	Irreversible
	Amenable to remote delivery	Alters reproductive behavior of treated individuals
	Equally efficacious to both sexes	
	Single chemical formulation efficacious across all vertebrate species	
	Rapid degradation	

oppose moralistic-based efforts of animal rights activists to substitute wildlife contraception for all hunting (fig. 6B).

Compromise

Left unmanaged, the wildlife contraception controversy will devolve into confrontational questions of *will we* or *won't we*. The challenge of the wildlife policy decision process will be to focus the debate on circumstantial questions such as *how will we* or *where will we.*

Currently, three distinctly different contraception technologies are being developed and tested for use in free-ranging wildlife populations: contraceptive steroids, immunocontraceptives, and chemosterilants such as hormonal toxins. Each technology has its advantages and disadvantages (table 2). Regardless of which technology is used, modeled responses of simulated populations suggest that applied wildlife contraception will be both prohibitively expensive and logistically daunting unless a single treatment endures for the reproductive lifetime of each treated individual (N. T. Hobbs, pers. comm.). Furthermore, the most efficacious treatments involved a combination of hunting (or culling) to lower population levels and contraception to maintain them at the desired level. In addition, the use of contraception to maintain wildlife populations is more precarious than shooting because much of the reproductive portion of the population has been uncoupled from density-dependent reproductive responses. Based upon what wildlife biologists now know, a prudent answer to the *how will we* question might be to control populations with both hunting and contraception.

Moreover, it seems unlikely that wildlife contraception will replace hunting as the wildlife population control of choice even if that were the most desired option. Hunting provides for an efficacious control on large-animal populations because an army of volunteer hunters not only donates its time but also pays for the opportunity. Consequently, hunting is not only effective, it is also economical. The niche for wildlife contraception most likely will be to control wildlife populations in areas such as nature preserves, wildlife parks, and urban open space, where control by licensed hunters is either impractical, undesirable, or unsafe (Hoffman and Wright 1990, Underwood and Porter 1991, Warren 1991, Curtis and Richmond 1992, Porter 1992).

Table 3. Contrasting characteristics of proactive *v.* reactive agencies

Proactive agencies	Reactive agencies
Driven by vision	Shackled by tradition
Committed to planning	Addicted to action
Planning anticipates the need for action.	Action precipitates a need for crisis planning.
Policy is by design: from the top down.	Policy is by default: from the bottom up.
Macromanagement: focuses on outcomes	Micromanagement: focuses on activities

Deflecting the wildlife contraception debate from confrontation to compromise will require a policy decision process that informs, educates, involves, and responds to the values of all stakeholders. Is the current process up to the challenge? Not without change.

In the first place, the current policy decision process is fundamentally reactive, not proactive. Wildlife agencies, for the most part reflect the philosophy, "if it ain't broke, don't fix it." Consider the contrasts between reactive and proactive organizations. Reactive organizations tend to be shackled by tradition and addicted to action. That action often leads to defensive planning. Policymaking tends to come from the bottom up, and there is a compulsion to micromanage activities and ignore or overlook the larger policy issues. In contrast, proactive agencies are driven by vision and committed to planning which, then, leads to action. Policy is formulated by design and implemented from the top down. Implementation is macromanaged by focusing on outcomes rather than activities (De Greene 1982, Gawthrop 1984, Morgan 1988). Reactive agencies look over their shoulders, fixed in their past. Proactive agencies, in contrast, scan the horizon in search of their future (table 3).

Attitudes of wildlife agency employees reflect a fixation on the past by clustering more closely toward traditional clients than toward the general public (Kennedy 1985, Peyton and Langenau 1985). For example, one of our Colorado surveys contrasted attitudes of bighorn sheep hunters, the general public, and Colorado Division of Wildlife employees. When asked whether they agreed or disagreed with the statement, *"Hunting male bighorn sheep is a form of sport and recreation, and people who want to hunt them should be allowed to do so,"* large majorities of both agency employees and bighorn sheep hunters agreed. In contrast, a substantial majority of the general public disagreed with the statement (fig. 7).

If most wildlife agencies are, indeed, fundamentally reactive, first and foremost they need to change their basic management philosophy from "if it ain't broke, don't fix it" to "if it ain't broke, break it" because management environments change constantly and management responses also must change constantly to keep pace. Wildlife agencies will have to break from their traditional biases to form effective partnerships with all of their publics to develop and evaluate truly *public* wildlife policies (Anderson 1975, Clark and Kellert 1988).

In the case of the pending wildlife contraception controversy, wildlife agencies still have an opportunity to be proactive. None of the developing technologies is yet operational. As a result, the management environment remains relatively unpolarized over the contraception issue. Thus, the future can be influenced and will depend largely on how agencies

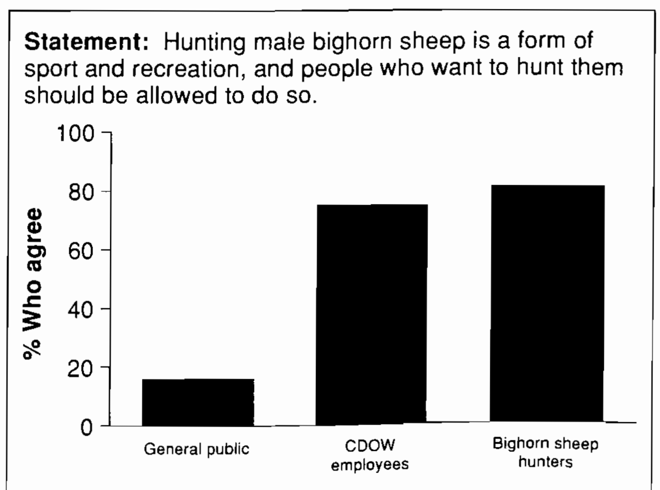

Figure 7. Contrasts between the attitudes of Colorado Division of Wildlife employees, bighorn sheep hunters, and the general public over whether bighorn sheep hunting for sport and recreation ought to be permitted.

respond to contraception as an emerging wildlife management tool. Proactive wildlife agencies dedicated to the overall public interest will respond with a combination of vision, wisdom, courage, accessibility, adaptability, and fairness.

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Directory of Personal Communication

Hobbs, N. T. Colorado Division of Wildlife, Wildlife Research Center, 317 W. Prospect Road, Fort Collins, CO 80526.

Appendix 1
Authors' Affiliations

Cheryl Asa, Ph.D.
St. Louis Zoo
1 Government Drive
Forest Park
St. Louis, MO 63110

N. J. Bean
Dept. of Psychology
Vassar College
Poughkeepsie, NY 12601

Susan E. Becker, M.S.
Rutgers University
Dept. of Animal Sciences
New Brunswick, NJ 08903

Mary Bomford, Ph.D.
Bureau Resource Sciences
P.O. Box E11
Kingston ACT 2604
Canberra, Australia

Mark P. Bradley, Ph.D.
Perth Zoological Gardens
20 Labouchere Rd.
South Perth, WA 6151
Australia

Kathryn Converse, Ph.D.
National Wildlife Health Center
U.S. Department of the Interior
U.S. Geological Survey, Biological Resources Division
6006 Schroeder Road
Madison, WI 53711

Phil E. Cowan, Ph.D.
Manaaki Whenua—Landcare Research
Private Bag 11052
Palmerston North, New Zealand

Paul D. Curtis, Ph.D.
Cornell Cooperative Extension
Dept. of Natural Resources
Room 114, Fernow Hall
Cornell University
Ithaca, NY 14853-3001

Daniel J. Decker, Ph.D.
Human Dimensions Research Unit
Department of Natural Resources
Cornell University
Ithaca, NY 14853

Janine A. Duckworth, Ph.D.
Manaaki Whenua—Landcare Research
P.O. Box 69
Lincoln, New Zealand

Bonnie S. Dunbar, Ph.D.
Dept. of Cell Biology
Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030

Richard A. Fayrer–Hosken, D.V.M., Ph.D.
Dept. of Large Animal Medicine
College of Veterinary Medicine
University of Georgia
Athens, GA 30602–7385

R. Bruce Gill, M.S.
Colorado Division of Wildlife
Wildlife Research Center
317 W. Prospect Road
Ft. Collins, CO 80526

Robin B. Goodloe, Ph.D.
U.S. Department of the Interior
U.S. Fish and Wildlife Service
4270 Norwich St.
Brunswick, GA 31520

David Guynn, Jr., Ph.D.
Clemson University
Lehotsky Hall
Clemson, SC 29634–1003

Heidi Hales
Dept. of Biology
University of Pennsylvania
Philadelphia, PA 19104

Cathleen A. Hanlon, V.M.D., Ph.D.
Centers for Disease Control and Prevention
Rabies Section, Mailstop G33
1600 Clifton Road
Atlanta, GA 30333

Simon E. Jolly, Ph.D.
5 Howitt Court
Werribee Vic 3030
Australia

Andreas Kappeler, Ph.D.
Institute of Pathology
University of Bern
Murtenstrasse 31
3010 Bern/Switzerland

Larry S. Katz, Ph.D.
Dept. of Animal Sciences
Cook College, Rutgers University
P.O. Box 231
New Brunswick, NJ 08903

James J. Kennelly, Ph.D.
National Wildlife Health Center
U.S. Department of the Interior
U.S. Geological Survey, Biological Resources Division
6006 Schroeder Road
Madison, WI 53711

Darrel J. Kesler, Ph.D.
Dept. of Animal Sciences
University of Illinois
1207 W. Gregory Drive
Urbana, IL 61801

Jay F. Kirkpatrick, Ph.D.
ZooMontana
P.O. Box 80905
Billings, MT 59108

Terry J. Kreeger, D.V.M., Ph.D.
Sybille Wildlife Research Unit
Wyoming Game and Fish Department
2362 Highway 34
Wheatland, WY 82201

Samuel B. Linhart, M.S.
Southeastern Cooperative Wildlife Disease Study
College of Veterinary Medicine
University of Georgia
Athens, GA 30602

I.K.M. Liu, D.V.M., Ph.D.
Dept. of Population Health and Reproduction
School of Veterinary Medicine
University of California
Davis, CA 95616

Cynthia A. Loker, M.S.
Human Dimensions Research Unit
Dept. of Natural Resources
Cornell University
Ithaca, NY 14853

J. Russell Mason, Ph.D.
USDA/APHIS/ADC/DWRC
Monell Chemical Senses Center
3500 Market Street
Philadelphia, PA 19104
Currently: Station Leader, Predation Ecology and Behavior
USDA/APHIS/National Wildlife Research Center
BNR-163, Utah State University
Logan, UT 84322

Lowell A. Miller, Ph.D.
USDA/APHIS/ADC
National Wildlife Research Center
1716 Heath Parkway
Ft. Collins, CO 80524-2719

Michael W. Miller, Ph.D.
Colorado Division of Wildlife
Wildlife Research Center
317 W. Prospect Rd.
Ft. Collins, CO 80526

Lisa I. Mueller, Ph.D.
Dept. of Agriculture and Natural Resources
Delaware State University
Dover, DE 19901–2277

Peter O'Brien, Ph.D.
Bureau Resource Sciences
P.O. Box E11
Kingston ACT 2604
Canberra, Australia

Milo E. Richmond, Ph.D.
New York Cooperative Fish and Wildlife Unit
Cornell University
Ithaca, NY 14853

Charles E. Rupprecht, V.M.D., Ph.D.
Centers for Disease Control and Prevention
Viral and Rickettsial Zoonoses Branch
1600 Clifton Road, MS-G33, Bldg. 15
Atlanta, GA 30333

Rebecca J. Stout, M.S.
Human Dimensions Research Unit
Dept. of Natural Resources
Cornell University
Ithaca, NY 14853

John W. Turner, Jr., Ph.D.
Dept. of Physiology and Molecular Medicine
Medical College of Ohio
3000 Arlington Avenue
P.O. Box 10008
Toledo, OH 43699-0008

C. H. Tyndale–Biscoe, Ph.D.
Research School of Biological Sciences
Australian National University
Canberra, ACT 2601
Australia

Robert J. Warren, Ph.D.
Warnell School of Forest Resources
University of Georgia
Athens, GA 30602–2152

L. Paige Willis, Ph.D.
Dept. of Large Animal Medicine
College of Veterinary Medicine
University of Georgia
Athens, GA 30602–7385

Lamar A. Windberg, M.S.
USDA/APHIS/ADC/DWRC
Predator Ecology and Behavior Project
Utah State University
Logan, UT 84322–5295

Index