An Analysis of the Feasibility of Using Fertility Control to Manage New Jersey Black Bear Populations

by

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EXECUTIVE SUMMARY

Reproductive Biology and Social Structure – Bears are long-day breeders, with most mating taking place in late-June and early July. Most cubs in a population[1] are sired by just a few dominant males, which tend to be large-bodied and aggressive. Females often mate with more than one male, and litters may be comprised of cubs sired by more than one male. Females often come into estrus and mate more than once in a season.

After fertilization, the zygote develops to a blastocyst (~300 cells), which floats in the uterine lumen until late November or early December, when it implants in the uterine wall. Late in the fall, there appears to be an endogenous physiological cascade in female bears, which prepares the uterus to implant one or more embryos, regardless of whether an embryo is actually present. This results in pseudopregnancy in sows that have not been impregnated. After a gestation period of ~55 days, pregnant sows give birth in the den to tiny, hairless, helpless cubs. The cubs nurse and grow in the den until they emerge in the spring. They remain with their mother for about 16 months, after which they are weaned. Soon after separating from her cubs, the female comes into estrus and mates again. Thus, a two-year reproductive cycle is normal.

Males compete aggressively with other males for the opportunity to mate with females. Dominant bears are large and often show physical evidence of fighting, such as scars and broken canine teeth, as a result of competition for females. The resident dominant males may impose limits on the immigration of other bears, particularly young males, into an area. Removing dominant males may alter the social dynamics of the bear population.

Bear Residency and Movements – Female black bears occupy relatively small home ranges during the breeding season in late spring and early summer. In some circumstances, these home ranges are defended and thus may be considered territories. When female yearlings become independent, at about 16 months, they usually settle in areas adjacent to or near the ranges of their mothers. In contrast, males often disperse long distances. The home ranges of breeding males encompass the ranges of several females. Outside of the breeding season, black bears of both sexes may move relatively long distances (i.e., tens of kilometers) to exploit seasonally abundant food resources.

Approaches to Fertility Control – A number of contraceptive methods have been developed for use in various mammals. These include hormone implants, surgical procedures, chemical sterilants, and vaccines. Of these, two are under active consideration for fertility control in bears: 1) Neutersol®, approved for use on male dogs, uses an injection of high concentration of the heavy metal, zinc. The testes of treated dogs undergo severe atrophy, spermatogenesis ceases, and serum testosterone levels fall. Neutersol® is expected to have similar effects on male bears, which will likely result in lowered social status of treated males. The treatment is permanent. (Sterilization of males by vasectomy is unlikely to affect male social status and libido, because testosterone levels would not be altered, although the procedure carries a greater risk of infection.) 2) pZP (porcine *zona pellucida*) vaccines have proven effective in several mammal species, including black bears. Females treated with pZP vaccines respond by producing antibodies that attach to the surface of their eggs, blocking sperm binding. Treated females may undergo repeated estrous cycles, but are otherwise unaffected. The pZP vaccines that have been shown effective in bears require boosting.

Limiting population growth by using fertility control is more likely to succeed if females, rather than males, are contracepted. This owes to three factors: 1) one male can inseminate many females, 2) each female often mates with several males during a breeding season, and 3) males disperse over large distances, while females tend to be more sedentary. Contracepting males is not an effective population control strategy.

[1] A **biological population** is a group of individuals that interbreed among themselves and that are generally isolated from individuals of other populations. Populations must be separated from one another by some barrier or impediment to movement. Several biological populations of bears live in New Jersey.

Black Bear Capture Techniques – Capturing an adequate proportion of the population for treatment is the main technical challenge and expense in applying fertility control agents to any population. Various sorts of traps have been used successfully for many years. The main difficulty is capturing a large proportion of the bear population in a specific area necessary to achieve population control. Treating a large proportion of the bear population would be extremely difficult and very expensive.

Regulatory Framework[2] – There are no approved fertility-control agents that are specifically approved for bears or any other mammalian wildlife species. However, AMDUCA (Animal Medicinal Drug Use Clarification Act) provides that most drugs approved for use in one species can be used in another, under the supervision of a veterinarian. For example, Neutersol®, which is approved for use in dogs and is being tested as an agent for sterilizing male bears in captive animals, could be applied to wild bears under the supervision of a veterinarian. Vasectomies could also be performed under existing regulations. pZP vaccines do not have regulatory approval. Whether the FDA (US Food and Drug Administration) would issue an INAD (Investigational New Animal Drug) exemption for a pZP vaccine specifically intended for bears is unknown. New Jersey state wildlife authorities would also have to approve the use of any fertility control agents or procedures.

Conclusions –

1) Immunocontraception, using a pZP (porcine zona pellucida) vaccine administered to females, has the best potential to control reproduction in individual female bears, while minimally affecting normal social dynamics. Neutersol® is very likely to be effective in sterilizing male bears, although treated males will be relegated to subordinate social status because of the effects of the treatment on hormone levels. (Males could, however, be vasectomized without affecting social structure and dynamics.)
2) Because one male can inseminate many females and because males tend to disperse more widely than do females, fertility control applied to females, is the most effective strategy for managing population size of wildlife species, including black bears.
3) Of the options presently being considered for bear fertility control, only Neutersol® and vasectomy have regulatory approval. Although pZP vaccines, which contracept females with minimal effects on treated animals, are best suited for wildlife population control, none has regulatory approval. Whether the FDA would permit field trials of pZP vaccines on black bears is unknown.
4) If all or most dominant male bears in a population are effectively removed from their social positions by sterilization with Neutersol®, it is likely that the consequential social disruption would allow an influx of young males, which would do much of the breeding.
5) Managing black bear populations using fertility control will be much more technically difficult and costly than in other wildlife species, such as deer and wild horses, where this approach has been successfully applied. This is a consequence of the difficulty of capture, lower density, and the variable and wide-ranging nature of bear movements.
6) Fertility control is very unlikely to be a feasible means of managing black bear populations in New Jersey.

[2] NOTE ADDED IN PROOF: In 2006, regulatory authority for contraception of wildlife and feral animals was transferred from the FDA to the EPA (Environmental Protection Agency). The implications of this change are not known at present.

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1 INTRODUCTION

The New Jersey black bear *(Ursus americanus)* population has been growing rapidly in both distribution and abundance in recent years (Carr and Burguess 2005). Although fewer than 100 bears, restricted to the northernmost part, are thought to have been present in the state in the 1950s, by 2001, the population was estimated at 1,777 in northern New Jersey and the range had expanded to occupy roughly the western two-thirds of the state. This is believed to be a consequence of protection afforded by game-animal status, which was conferred on bears in 1953, and of the maturation of young forests in the state, leading to improved habitat and food supply (e.g., hard mast). Natural food is supplemented by food of human origin, such as garbage and agricultural crops. The expanding bear population has led to an increasing number of conflicts with humans in New Jersey.

The New Jersey Department of Environmental Protection, Division of Fish and Wildlife, has regulatory authority for managing the state's bear population. Hunting, which can both control numbers and result in aversive conditioning of bears (Geist 2005), has become controversial. Better management of garbage, bird feeders, and other bear attractants could help to reduce human-bear conflicts. However, conflicts are bound to increase if the bear population continues to expand. In 2004, United States state wildlife agencies reported a perceived 45 % increase in expenditures to control bear-related damage, a 22 % increase in personnel-hours to resolve bear-related complaints, and a 19 % increase in the overall number of complaints over the previous 5 years (International Association of Fish and Wildlife Agencies 2004).

The size of a wildlife population is governed by just 4 basic factors: 1) fertility, 2) mortality, 3) emigration, and 4) immigration. Emigration and immigration are difficult to control and have little potential as tools to affect bear populations in a particular area, although the removal and long-distance displacement of individual problem bears is a common practice in many jurisdictions. Mortality and fertility can potentially be manipulated to affect the size of particular populations. In the past, the size of game animal populations, has been managed largely by adjusting the harvest, and a large body of information about this approach has developed over the years. On the other hand, over the past 25 years, managing wildlife populations by controlling fertility has been a focus of considerable interest (Fagerstone 2002). Despite this interest, however, fertility control (FC) has been applied in few situations, so little practical experience exists – none of it involving bears. Nevertheless, several things are clear:

1) The contraceptive agent must be long lasting (i.e., multi-year contraception from a single dose) to avoid the repeated stress on animals and the high cost of re-treatment.
2) Because most wildlife species are promiscuous, with each male capable of inseminating many females, FC methods that target males are virtually certain to fail.
3) A large proportion of the reproductive females in the population to be controlled must be treated, although the exact proportion will depend on whether the objective is to stabilize the population or to cause a decline.
4) FC programs are expensive because they are labor-intensive, and it is the cost of skilled labor and support involved in the capture (and recapture or re-treatment) of the animals that accounts for most of the cost. Monitoring and evaluation are also necessary to determine the effectiveness of any FC application.

5) There are no commercially available fertility-control agents that have regulatory approval and that meet the needs of a wildlife population management program.
6) Controlling reproduction is very difficult in free-ranging wildlife species with high reproductive potential and long life spans (Merrill et al. 2003).
7) Reducing populations by FC alone is, at best, slow and expensive.

The overall purpose of this report is to examine the feasibility of using fertility control to manage the size of the New Jersey black bear population. In the following sections, we review the following:

1) reproductive physiology of black bears, which will help to identify appropriate FC methods,
2) home range and movement patterns of black bears to provide a context in which to understand how the various FC options might be applied in the field,
3) capture techniques that can be applied to black bears, and
4) the available FC technology that has been tested in mammals and that might be applied in bears.

It is critical to understand that there are 3 factors that are essential to the successful application of an FC program. First, there must be an effective FC agent. Second, a practical, economical means must be available to deliver the FC agent to the animals that have to be treated. No matter how effective the FC agent, if it is impractical or exorbitantly expensive to deliver it to the animals, the program will fail. Third, the population to be controlled must have characteristics that lend themselves to this approach. That is, the population should be "closed", with little or no immigration from elsewhere, and composed of individuals that are easily captured.

Black bears are the most widely distributed members of the mammalian family Ursidae in North America. Formerly ranging from northern Mexico to Alaska and across the contiguous United States, American black bear populations are now fragmented from habitat loss and past excessive harvest. Because remnant populations are now separate and isolated, they are more likely to experience fluctuations in numbers (Hellgren et al. 2005).

Black bears are widespread in New Jersey, having been reported recently in every county (DFW 2004). However, the majority, an estimated 1,100 to 3,000 bears, inhabit the northwestern part of the state. Since the 1980s, black bear numbers have increased and the species' range has expanded. Bear populations have increased, not only in New Jersey, but also in nearby Pennsylvania and New York, due in large part to improved habitat provided by the maturation of forested areas (McConnell et al. 1997). The New Jersey Division of Fish and Wildlife, and the Fish and Game Council (i.e., the two state bodies charged with black bear management), manage black bears to assure their continued well-being, so that they can provide recreational opportunity and esthetic benefit for the citizens of New Jersey through hunting, photography, and observation (Carr and Burguess 2003). The first black bear hunt in 33 years, occurred during December 2003, with 328 bears being harvested.

Bears are resourceful creatures, taking advantage of "unnatural" foodstuffs when opportunities present themselves. Often these resources are provided by humans, either deliberately (e.g., baiting) or unintentionally (e.g., improper garbage containment and disposal, bird feeders; Beckmann and Berger 2003). The long-term, habituated attraction to unnatural food sources is termed "food-conditioning" (McCarthy and Seavoy 1994, Whittaker and Knight 1998). If food resources are plentiful, some bear populations may become overabundant and habituated, resulting in human-bear conflicts. When bear populations grow and expand into human-dominated landscapes, bear-people interactions often increase, resulting in more nuisance complaints. Bear conflicts escalate when animals become habituated to humans, especially if bears view human activity as being closely tied to easily attainable food. Bears often display uncharacteristically bold behavior to exploit these new-found resources, damaging property, and sometimes even threatening human safety (Weaver et al. 2003).

Nuisance bears pose a significant problem for wildlife managers. Threats to human safety and property by intruding bears may require immediate, and sometimes lethal, action. Professionals within wildlife agencies continue to investigate non-lethal methods for discouraging unwanted behaviors in nuisance bears. Such negative reinforcement is generally referred to as "aversive conditioning." Currently, translocation (McArthur 1981; Brannon 1987) and aversive conditioning (Polson 1983; McCarthy and Seavoy 1994; Ternent and Garshelis 1999; Clark et al. 2002; Rauer et al. 2003) are the most frequently used non-lethal management techniques. However, these methods are often unreliable, and if non-lethal approaches fail, it is often necessary to kill problem bears.

Translocation, or the trapping and subsequent release of an individual bear outside of its home range, has been a widely used technique for dealing with nuisance bears. Black bears (McArthur 1981) and grizzly bears, *Ursus arctos horribilis*, (Brannon 1987) have both been relocated because of nuisance activity. The success of these translocations has been highly variable, depending on the distance an individual was moved, physiographic barriers between release and capture site, elevation gain, and age and sex of the animals moved (McArthur 1981; Brannon 1987). Success rates of 63-76% have been reported for preventing further nuisance activity by black bears, while only 31-52% of relocations up to 117 km, prevented the individual from returning to its original home range (McArthur 1981). Translocation has been shown to be 57-65% successful in preventing further nuisance activity in grizzly bears (Brannon 1987). Translocation is expensive and time consuming; furthermore, it is often necessary to relocate an individual multiple times (McArthur 1981; Brannon 1987). Nevertheless, this remains one of the most widely used management techniques because there are few other non-lethal options.

The use of rubber bullets or rubber buckshot to inflict ephemeral pain, and cracker shells (pyrotechnic and noise making devices) fired from 12-gauge shotguns to scare problem bears, have also become common techniques to deter nuisance activity (Rauer et al. 2003). After aversive conditioning treatment, it is expected that a problem bear will associate pain and a sense of fear with humans, thereby decreasing nuisance activity (McCarthy and Seavoy 1994). Few projects have critically examined this type of aversive conditioning. Rauer et al. (2003) is a notable exception. They reported highly variable success rates in preventing further nuisance activity in European brown bears (*Ursus a. arctos)*. Bear behaviors were scattered along a continuum ranging from no change in behavior, to a long-term avoidance of humans, but were heavily skewed towards the unsuccessful side (Rauer et al 2003).

On-site capture and release has also been studied as a potential tool to aversively condition bears. The negative stimuli provided by the capture and handling of the problem individual at the site of the nuisance activity reinforces the bear's natural fear of humans, resulting in avoidance of the area (Clark et al. 2002). This has been shown to be very successful in precluding problem bears from repeating nuisance behavior at the site of capture (Wooding et al. 1994; Clark et al. 2002). However, these investigators discussed avoidance of the capture site only, and neglected to report the efficacy of the method in relation to nuisance activity by treated bears in other areas. This method would need further investigation before it could be considered viable.

Because nuisance activity and complaints may be associated with bear abundance, reducing bear populations in areas with frequent conflicts may be a long-term management goal. If wildlife populations cannot be managed directly by harvest, then fertility control may help limit population growth. However, bears are long-lived and typically give birth to 2-3 cubs (see *Reproductive Biology* below). For other large mammals with similar reproductive characteristics (e.g., white-tailed deer, *Odocoileus virginianus*), controlling reproduction has proven quite challenging (Merrill et al. 2003).

2 REPRODUCTIVE BIOLOGY

Black bears are long-day breeders, with breeding activity peaking in late June or early July, although mating can occur between mid-May and September (Spady, in review, Pelton 2003, Rogers 1987, Jonkel and Cowan 1971). For example, in Virginia, about 75 % of the females >2 years old were in estrus during the first 10 days of July (M. Vaughan, pers. comm.). The onset of breeding activity appears not to vary much with latitude in North America; however, the breeding season tends to extend later in more southerly areas (Garshelis and Hellgren 1994). Rogers (1987) has suggested that the breeding season may be particularly constrained in northern areas by the period of hyperphagia and the requirement to acquire the fat stores needed to survive the winter denning period.

The age at first reproduction in females probably varies according to nutrition and body size, so one would expect bears in poorer habitats to mature later than those in better habitats. Jonkel and Cowan (1971) observed no bears younger than 4.5 years in estrus in their Montana study area. However, Rogers (1987) and Vaughan (pers. comm.) have observed females breeding at 2.5 years, just 1 year post weaning, in Minnesota and Virginia, respectively. In New Jersey, where food is abundant and the population is expanding into new areas, we would expect females to both have large litters and breed at an early age. The length of estrus in female black bears is only a few days. Rogers (1987) found the longest that any of 20 females in his Minnesota study area was receptive was just 3 days, although they attracted males over a period of up to 5 days. However, females may go through multiple estruses each season (see below).

The age at first reproduction for males is less certain. Because large males dominate the breeding activities and actively pursue receptive females (Kovach and Powell 2003), subordinates may not have the opportunity to mate when they are physiologically first capable, which can occur as early as 1.5 years, as evidenced by mature spermatids (Erickson and Nellor 1964). The removal of dominant boars would probably lead to earlier breeding among younger males.

The pattern of increase in serum testosterone in bears from pre-emergence through the breeding system is not entirely clear. Although Palmer et al. (1988) and McMillen et al. (1976) reported that males emerging from their dens had near-maximal testosterone levels, Garshelis and Hellgren (1994) and Tsubota et al. (1997) report a pattern of increasing readiness for breeding following emergence and continuing up to the breeding season, as measured by increasing serum testosterone levels. Testicular recrudescence begins in the winter den, but is not complete until the breeding season begins. Tsubota et al. (1964) reported that spermatozoa were present in June, but not in January (denning period), March (pre-breeding), or October (post-breeding). Erickson and Nellor (1964) found mature spermatids in testes of bears killed in April, but not earlier. Until the end of the breeding season, males show little tolerance of other males and fighting may occur, particularly among large, dominant individuals, for access to females. Following the breeding season, the boars' testes regress in size, becoming abdominal, serum testosterone falls to very low levels, and spermatogenesis ceases (Tsubota et al. 1997, Garshelis and Hellgren 1994). The testes are at their smallest when the bears enter hibernation, but begin to recrudesce in January, reaching the maximum size in May (Howell-Skalla et al. 2000, Garshelis and Hellgren 1994).

Among the males, access to females for breeding is governed by a dominance hierarchy. This hierarchy is apparently related to age and size (Kovach and Powell 2003, Barber and Lindzey 1986). In some situations, (e.g., Long Island, Washington), the dominance hierarchy may be well-enough established that dominant animals can displace subordinates without fighting (Barber and Lindzey 1986). However, in other areas (e.g., Great Dismal Swamp, northern Minnesota, and western North Carolina) fighting is common and many bears carry wounds (Kovach and Powell 2003, Rogers 1987). During the breeding season, males often show evidence of serious injury.

Garshelis and Hellgren (1994) found that as the breeding season commenced, serum testosterone levels rose in the dominant males, which were also larger and older individuals. As a group, the 3-year-olds were the least successful during fights with older bears, were very likely to carry wounds, and had relatively low testosterone levels. In some other bear species, it has been observed that testosterone levels fall in individuals that are unsuccessful in competing for status or territories (Bartsch et al. 1992, Hellgren et al. 1989). Garshelis and Hellgren (1994) contend that the secretion of testosterone is modulated through social interactions among males.

The length of time that males can remain in a position of dominance is probably 3-4 years, (E. Hellgren, R. Powell, L. Rogers, M. Vaughan, pers. comm.). Males do not reach full size until they are 5 or 6 years old, and bears older than 8 have reduced testosterone levels (Garshelis and Hellgren 1994). The benefit to males who become dominant appears to be considerable, in an evolutionary sense. Kovach and Powell (2003) found that 91 % (20 of 22) of cubs in 7 litters had been sired by just 3 dominant males in their North Carolina study population.

During the peak of the breeding season, the dominant males are very active and may reduce the amount of feeding that they do (Garshelis and Hellgren 1994, Coy and Garshelis 1992, Rogers 1987). These males may exhaust themselves during the period of greatest breeding activity and then retire, allowing the younger subordinates to have opportunities to mate later in the season. A similar pattern has been observed in red deer *(Cervus elaphus)* (Clutton-Brock et al. 1982) and in fallow deer *(Dama dama)* (M. Fraker, pers. obs). The tendency for a majority of female black bears to come into estrus during the peak early in the breeding season and to mate with a number of males at that time may limit the number of females that do not conceive and come into estrus later. However, some females may go through more than one estrus (Spady et al. in review).

Spady et al. (2006) have conducted a comprehensive review of all available information, published and unpublished, on reproduction in the Ursidae. They found evidence of multiple estruses in both free-ranging and captive bears of all species, except the sun bear *(Helarctos malayanus).* During a given breeding season, black bears may exhibit as many as three estruses, separated by periods of up to 45 days when the animals are non-receptive (Spady et al. 2006, Kovach and Powell 2003, Eiler et al. 1989). Craighead et al. (1995) showed female grizzlies that copulated most often also were observed with the largest number of cubs, apparently as a result of conceptions resulting from multiple matings during different estruses. Thus, unlike most other female mammals, which go though multiple estruses only if they fail to conceive during the first, female bears may undergo multiple estruses regardless of whether they have conceived. This may be possible owing to the inactivity of the *corpora lutea* following fertilization, which would otherwise inhibit ovulation.

Bears probably are induced ovulators, although this has not been proven unequivocally. If true, coital stimulation would be necessary for ovulation to take place (providing that mature follicles are present) (Boone et al. 2004, 1998). Following fertilization, the resulting zygote develops to the blastocyst stage (approx. 300 cells), after which further development is arrested (embryonic diapause) for several months (Erickson and Nellor 1964, Wimsatt 1963). The blastocysts remain in the lumen of the uterus until they implant in late November or early December, soon after the animals enter hibernation.

Female bears can demonstrate "pseudopregnancy" in which they undergo the hormonal changes and other phenomena associated with pregnancy, whether or not they are pregnant (Spady et al. 2006). These changes occur at about the time that the bears enter hibernation, possibly triggered by prolactin that is induced by changes in photoperiod (i.e., short days) (Sato et al. 2001). Seasonal reactivation of the *corpora leutea* may have evolved to ensure that the uterus is prepared for implantation at the proper time in the absence of signals from the conceptus (Spady et al. 2006). In the case of pregnant females, the embryo implants in the uterine wall and resumes development. Those females that are not pregnant continue to show the hormonal changes associated with pregnancy over the course of the normal gestation period. Other seasonal breeders that exhibit delayed implantation, particularly members of the mustelidae, also show pseudopregnancy (Spady et al. 2006).

The cubs are born in late January or early February after a gestation of about 55 days (Pelton 2003). At birth, the cubs are helpless, naked, and tiny, measuring only 20 cm in length. Much of their growth and development takes place in the den before they emerge in the spring. Litters of 2-3 are the most common, but 6 cubs were observed in one New Jersey litter (K. Burguess, pers. comm.). Cubs remain with their mothers until they reach about 16 months of age, when they are weaned. The female demonstrates lactational anestrus during the first summer of her cubs' life, but mates soon after her cubs are weaned (Rogers 1987, Jonkel and Cowan 1971). Thus, reproduction in black bears normally follows a 2-year cycle. Rarely, a female may mate and become pregnant in the same year in which she has given birth (Lecount 1983).

Dogs, which, like bears, are Arctoid carnivores, also demonstrate pseudopregnancy (Gobello et al. 2001). However, the characteristics of pseudopregnancy in the two groups differ in significant respects (Table 1). In the case of dogs, which are social carnivores derived from wolves, pseudopregnancy results in maternal changes, including nesting behavior, mammary enlargement, and lactation. Pseudopregnant canines can serve as "wet nurses", and this may have been the adaptive function of pseudopregnancy – the provision of pack members who could assist the alpha female in rearing her pups.

Table 1. A comparison of characteristics of pseudopregnancy in bears and dogs.

Characteristic	Dogs	Bears
Pseudopregnancy immediately follows coitus	yes	no
Pseudopregnancy is seasonal	no	yes
Pseudopregnancy inhibits mating behavior	yes	no

3 HOME RANGE AND MOVEMENT

Understanding how bears use the landscape is essential to understanding the potential for FC to be a useful tool to control populations. Mature females usually hold and defend territories from which all other adult females are excluded, particularly during the period following emergence from the den in the spring until the conclusion of the breeding season in the summer (Rogers 1987). In late summer and fall, females and their dependent cubs often range well outside of their home ranges to forage on locally abundant food sources. Male home ranges overlap to a large extent with those of other males and encompass the territories of several females. Males engage in marking behavior and establish dominance hierarchies among themselves, but do not defend territories.

Information on female home range sizes and areas of concentrated use are crucial to understanding a bear population's spatial requirements. Habitat quality (Jonkel and Cowan 1971) and population density (Oli et al. 2002) have both been associated with home range size. Territoriality may also be based on habitat quality, which in turn can be a function of regional climate (Horner and Powell 1990).

Home range size has been reported to be highly variable among different black bear populations (Oli et al. 2002, Hirsch et al. 1999, Grogan 1997). Oli et al. (2002) reported the mean home range size for adult females in Arkansas's bottomland hardwood forest to be 4.90 km^2, whereas Grogan (1997) documented an average range size of 137 km^2 for adult females in the Snowy Range of Wyoming. Mean home range sizes for most other black bear populations fall between these 2 extremes. For example, Hirsch et al. (1999) recorded an average home range size of 48 km^2 in northern Michigan.

Age and sex classes also influence home range size. Average adult female home ranges were significantly smaller, sometimes <25%, than that of males (Hirsch et al. 1999). Grogan (1997) further surmised that subadult males and females occupied smaller home ranges than their respective adult counterparts.

Oli et al. (2002) reported that home range sizes in Arkansas were related to population density. During 1980 to 1994, a period of rapid population growth, population density and size of female home ranges were negatively correlated. Habitat quality and population density apparently impact home range size, but the relative importance of these factors depends on the region and/or population. In New Jersey, female home ranges have diminished in size, possibly as a consequence of increasing numbers and density of bears (DFW 2004). In the early 1990s, female territories averaged about 16.5 km^2 in prime habitat, but 10 years later, average territory size had declined to about 5 km^2.

Home range overlap was more common in areas with adequate food resources (Horner and Powell 1990). Oli et al. (2002) found a mean of 1.01 km^2, or 22.7%, of mean annual home range size of females to be shared with other females in Arkansas. Shenk et al. (1998) also reported "extensive home range overlap" among females. Rogers (1987), however, described defended territories that were the exclusive domain of particular adult females following emergence from dens and through the breeding season in his Minnesota study area. Aggressive interactions and chases were involved in the establishment of boundaries. As bears died and left the population or new animals were recruited, the size and shape of the existing territories changed. Daughters often settled in areas that were adjacent to or part of their mothers' territories.

Rogers (1987) suggested that male mating ranges and movement patterns should enable the efficient monitoring of potentially estrous females. The mating ranges of the males in his study area encompassed at least part of 7-15 female territories.

Following the breeding season, both males and females travel more widely to feed on locally abundant food resources and become more tolerant of others of the same gender (Rogers 1987). At this time, females do not pursue trespassers and they often pass through the territories of other females. Between 10 July and the denning period, 69 % of males and 40 % of females foraged >7 km outside of their usual ranges for more than a week in Rogers' (1987) Minnesota study area. Females ranged as far as 83 km and averaged about 30 km. Males traveled farther, with one male making an excursion of 200 km. These late summer and fall travels, which occur during the period of hyperphagia, take the bears into areas where food is more abundant. In the presence of abundant food, defense of the resource is unnecessary.

4 APPROACHES TO FERTILITY CONTROL

Introduction: General Strategies

Methods of contraception rely on 1) the control of physiological mechanisms that regulate production of reproductive hormones, 2) gonad function and gamete production, 3) oöcyte fertilization and implantation, or 4) the maintenance of pregnancy. Contraceptive drugs interfere with reproductive functions at the hormonal level and require repeated application to maintain control. Some have been adapted in slow-release formulations to control fertility over longer periods without frequent intake of the active ingredient. Vaccines, on the other hand, have the ability to direct the immune system to a given target over considerably longer periods ranging from a few months to many years. When treating wildlife species, access to individuals is typically difficult and expensive, so that only long-lasting, single-administration treatments are practical for field application.

Over the last 25 years, contraceptive vaccine development has focused on fertility control of humans, livestock, companion animals, and wildlife (including pest species). The requirements for the various applications differ significantly: a human contraceptive vaccine must be equivalent to current methods of contraception, which are nearly 100 % effective for a given period, followed by a restoration of fertility. Efficacy requirements for companion animals are equally stringent. However, the efficacy requirements for a livestock or a wildlife are more forgiving, preferably >90 %. Production animals destined for slaughter generally require fertility control for relatively short periods.

Contraceptive vaccines can be directed against hormones involved in reproduction and their receptors. The majority of research in this area focuses on gonadotropin-releasing hormone (GnRH), follicle stimulating hormone (FSH), and leutenizing hormone (LH), all of which control reproductive functions in both males and females. Therefore, vaccines against these targets are effective in both sexes. These hormones may control sexual behavior, and an effective vaccine will have the added benefit of diminishing aggressive behavior and libido in males and estrus in females. However, these characteristics may be undesirable when controlling a wildlife population as they can profoundly affect social structure.

A number of candidates for vaccines that control fertility without affecting sexual behavior have also been identified. These targets are generally involved in fertilization and implantation. Human chorionic gonadotrophin (hCG), is necessary for the establishment and maintenance of pregnancy, and has been successfully tested in women (Talwar 1997). Sperm surface antigens that can block sperm functions and inhibit fertilization have also been identified as vaccine candidates. Proteins derived from the oöcyte coat (zona pellucida = ZP) have been successfully used in vaccines to induce infertility in females of many species by producing antibodies capable of blocking fertilization and/or implantation (Gupta et al., 2004). The majority of these vaccines are designed to be used in females.

Contraceptive Vaccines

Hormone-based vaccines

A vaccine approach aimed at raising an immune response against any component of the hypothalamus-pituitary-gonad (HPG) axis has the potential to block fertility. The rationale is that antibodies directed at the hormones or their receptors have the ability to block signal transmission by the hormones and stop the signal cascade transmitted through the HPG axis (Fig.1).

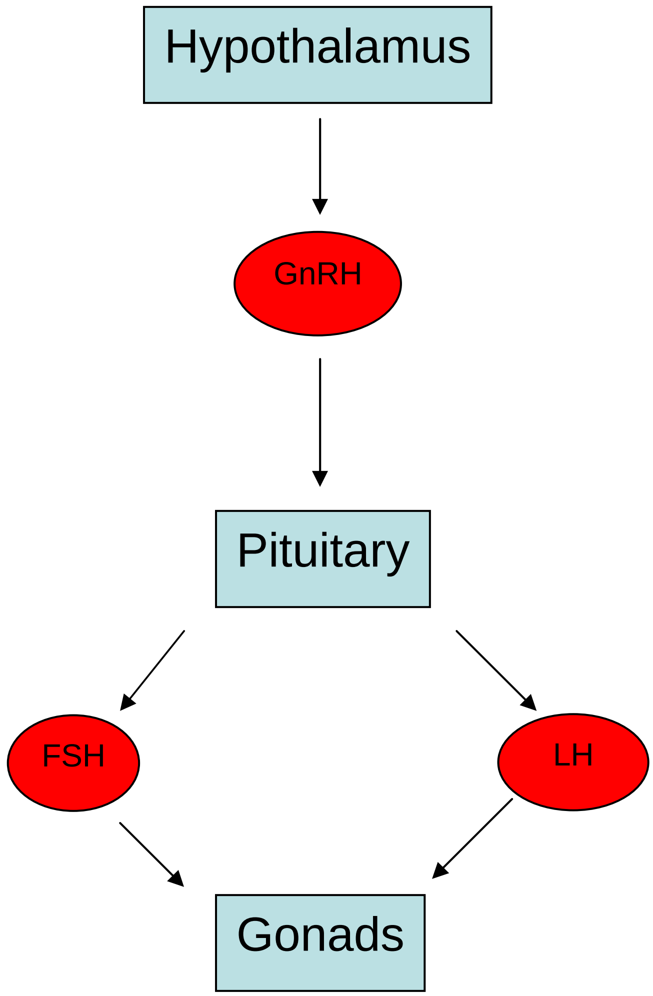

Figure 1. Schematic diagram of the hypothalamus-pituitary-Gonad (HPG) axis. GnRH produced by the hypothalamus regulates the production of FSH and LH from the pituitary. Gonadotropins control gamete production and gonadal steroidogenesis in males and females.

GnRH (gonadotropin-releasing hormone) is a10-amino acid hormone produced by the hypothalamus. It plays a critical role in reproduction and has been the target of many attempts to control fertility. GnRH induces the production of two gonadotropins by the pituitary: 1) follicle stimulating hormone (FSH), and 2) luteinizing hormone (LH). The gonadotropins in turn act on the gonads and control gamete production and sex hormones in both males and females. Since GnRH is at the top of the hypothalamic-pituitary-gonadal (HPG) axis (Fig.1), strategies to regulate this hormone can have profound effects on gametogenesis, sex hormone production, and hence fertility. Additionally, as a result of suppression of testosterone in males and progesterone in females, a block in the normal function of GnRH results in profound behavioral changes: males become less aggressive and females stop displaying the common signs of estrus. Secondary sexual characters are also affected, such as antler growth in male deer.

Gonadotropin releasing hormone (GnRH)

A vaccine targeting GnRH produces neutralizing antibodies that block the hormone cascade at the anterior pituitary gland level. GnRH-based vaccines have been tested in humans for the control of prostate cancer and hormone disorders, but their use for fertility control has been studied more extensively in domestic (cats and dogs) and production animals (i.e., cattle and hogs). GnRH-based vaccines produced in Australia have been commercialized in limited jurisdictions: Improvac™ for immunological castration of male pigs and the control of boar taint (Pfizer Animal Health Australia), Equity™ (Pfizer Animal Health Australia) for the control of estrus-related behavior in fillies and mares, and Vaxstrate™ (Arthur Webster Pty Ltd, Australia) for fertility control of heifers (no longer marketed). GnRH-based vaccines have also been tested in wildlife species, namely wild horses, bison, and deer (Stout et al. 2004, Miller et al. 2004, 2000). In wild horses, multiple immunizations were used and short-term efficacy (weeks to a few months) was achieved in some, but not all, horses (Stout 2004). In bison, one GnRH vaccination was effective for 6 months (Miller et al. 2004). Antibody titers dropped soon after and the cows were not bred in the second year. In deer, multi-year efficacy was achieved in a small study group, but a primary inoculation and two boosters were required in year one, followed by two boosts in year 2 (Miller et al. 2000).

It is difficult to elicit anti-GnRH immune responses by vaccination. To overcome this problem, GnRH is usually linked to highly immunogenic carriers such as keyhole limpet hemocyanin (KLH) or toxoids to increase its immunogenicity and sometimes aggressive adjuvants are used to formulate the vaccines (Delves 2004). Other more elegant approaches include the generation of multiple GnRH repeats, linking the GnRH peptide to specific immune-cell-activating peptides (T-helper epitopes) and synthesizing the reverse peptide to be used as an antigen to produce cross reactive antibodies (Robbins et al. 2004, Ghosh et al. 1999, Fromme 2003). Multiple immunizations are typically necessary to ensure lasting antibody levels that are effective in controlling fertility beyond one year. Most GnRH vaccines produce GnRH-specific antibodies for only a few months, even after multiple immunizations. To be effective for controlling wildlife populations, a long-lasting, single-dose vaccine would be necessary.

One GnRH vaccine, designed by Levy et al. (2004) as a single-immunization product, showed limited success in cats. Although the contraceptive effect in responding animals was maintained for 6 months, not all animals were able to generate sufficient anti-GnRH antibodies to confer contraception. A single dose of the same vaccine was administered to a small group of bison proved effective in all vaccinated animals for at least 6 months (Miller et al. 2004). Efficacy was confirmed by mating the immunized cows to a fertile bull. Anti-GnRH antibody titers in this case decreased 8 months post-vaccination, suggesting that the contraceptive effect was unlikely to be maintained beyond 1 year without boosting.

The efficacy and duration of antibody responses generated by a GnRH vaccine are species specific. A vaccine that was highly effective in rodents was considerably less durable and less efficacious in sheep and dogs (Ferro et al. 2004). GnRH is clearly a promising target for animal immunocontraception as long as the changes associated with the lack of sex hormones, often desirable for companion animals and livestock, do not adversely affect the social behavior and well-being of treated individuals in wildlife populations.

Unlike other hormones, GnRH is very small and extremely conserved (i.e., virtually identical) among all mammalian species. Consequently, GnRH is only weakly antigenic. Because GnRH constitutes a reproductive switch in both males and females, an effective GnRH-based vaccine may be "universal" for fertility control of males and females of any mammalian species. The efficacy of current GnRH vaccines, however, needs to be greatly improved to ensure a high responder rate, and to provide long duration of contraception in the target species.

Follicle stimulating hormone (FSH)

The gonadotropin FSH is produced by the pituitary in response to GnRH stimulation (Fig. 1). FSH plays an important role in gamete formation/maturation in both males and females. FSH-based vaccines in females disrupt follicle maturation and result in ovarian failure. Because of this irreversible sterility and consequential hormone imbalance, FSH vaccine research has focused on males.

Immunization with FSH in males is considered safe based on multiple immunizations performed in laboratory animals and primates, including humans (Naz 2005). The FSH vaccine was further refined by using the beta subunit of the gonadotropin, which was effective by itself, while eliminating the occasional restoration of fertility associated with immunization with a FSH antigen that has full biological activity. The beta subunit could be produced by recombinant means for large-scale production without resorting to an animal source. Despite these advances, the efficacy of the vaccine was variable. FSH vaccines could exert only a partial effect, causing a reduction of up to 75% in sperm counts (Moudgal et al. 1997 a,b). FSH controls the production of primary spermatocytes but has no effect on spermatid formation at later stages, resulting in only a reduction in sperm counts and hence partial infertility. Since sperm production and function were not entirely eliminated, some of the sperm remained active and a portion of vaccinated males remained fertile. Adult hamsters and rams responded to FSH vaccination, but in rats, only immature animals (not adults) showed reduced fertility. Consequently, an FSH-based vaccine must be tested empirically in the target species. Because of the relatively low immunogenicity of FSH, a minimum of 4 immunizations are required to ensure efficacy (Moudgal 1997c). Further research is needed to enhance the immunogenicity of FSH and to confirm the efficacy of the FSH vaccine in adult males of target species.

Vaccination with FSH, or FSH receptor-based antigens, is reversible in the male, and fertility is usually restored when antibody levels drop below a certain threshold. In females, however, vaccines targeting FSH or its receptor may cause irreversible sterility. While this may be unacceptable for the management of some wildlife species, it may be acceptable or even desirable in some situations.

Luteinizing hormone (LH)

Similar to FSH, LH consists of alpha and beta subunits and is produced by the pituitary in response to GnRH. LH controls gamete maturation and sex steroid production by the gonads. Vaccines targeting LH or its receptor have the ability to block gamete production and control sex-associated behavior in males and females. The first generation of LH vaccines relied on purified ovine LH, which proved to be unsafe (Moudgal et al. 1997a). Although non-human primates exhibited azoöspermia (lack of sperm) and reduced testosterone levels, immunized animals developed alopecia and significant muscle loss, possibly as a result of cross-reactive antibodies that interfered with the alpha subunit of thyroid stimulating hormone (TSH). These adverse effects were circumvented when the beta subunit of LH alone was used as an immunogen, and long-term repeated immunizations with this antigen were safe in primates (Thau 1987). Unfortunately, the levels of anti-LH antibodies were incapable of effectively neutralizing endogenous LH in all vaccinated animals. Furthermore, the expected effect of LH immunization on sex hormone production rendered LH-based contraceptive vaccines undesirable for human use, and most LH vaccine research has been abandoned.

LH is a weak antigen (weaker than FSH) and numerous immunizations are required to maintain anti-LH antibody levels. As an alternative to LH, the LH-receptor (LHR) has been targeted in baboons, rabbits, dogs, cats, and rodents with mixed results (Pal et al. 1992a,b, Saxena et al. 2002 and 2003, Remy 1993, Singh et al. 1995). Immunization with a bovine LHR vaccine was well tolerated, but partial contraception was achieved only after multiple immunizations (typically 4). The contraceptive effect was also delayed in most species, requiring 3-4 months to become established. Unfortunately, the use of LHR from a bovine source, although plentiful, is not favored by regulatory agencies owing to risks of disease transmission, particularly bovine spongiform encephalopathy (BSE or “mad cow disease”).

Human chorionic gonadotropin (hCG)

Human chorionic gonadotropin is composed of alpha and beta subunits. Unlike the other hormones, however, hCG is pregnancy specific and is detected in circulation in females only after oöcyte fertilization. As hCG travels from syncytiotrophoblastic cells to the ovaries, it can be eliminated by antibodies and as a result, progesterone secretion required for establishment and maintenance of pregnancy is abolished (Delves 2004). hCG-based vaccines are, therefore, contragestational rather than contraceptive.

In one approach, the entire beta subunit of hCG was purified from the urine of pregnant women and used in a vaccine. Beta-hCG was coupled to tetanus toxoid to increase its immunogenicity and break tolerance toward the self antigen. In another approach, the region of beta-hCG corresponding to the C-terminal 37 amino acids was preferred because this region is specific to hCG. This antigen, known as CTP (carboxy terminal peptide), was coupled to diphtheria toxoid to increase its immunogenicity. After repeated immunizations, both candidate vaccines induced anti-hCG antibodies, which subsequently declined, allowing full recovery of fertility in immunized subjects. The use of the entire beta-hCG resulted in better antibody responses than those obtained with CTP, even when stronger adjuvants were used with the latter. hCG is the only anti-fertility vaccine target that has reached phase II clinical trials in humans (Naz 2005).

Phase I clinical trials were performed internationally with the beta-hCG coupled to tetanus toxoid (Talwar 1997). While the vaccine was well tolerated, efficacy was variable even after repeated immunizations. An improved version of the vaccine in which the beta-hCG was covalently linked to the alpha-ovine hCG to create a heterospecies dimer (HSD) underwent phase II clinical trials, but no added benefit was observed (Talwar 1997). Clearly, large improvements must be made to the hCG vaccine before it could be used as a contraceptive in humans. The use of such a vaccine for the control of animal populations is doubtful given that hCG is limited to higher primates.

Non-hormone Vaccines

Sperm antigens

The use of sperm proteins as vaccine antigen candidates is applicable in both males and females. Several lines of evidence show that sperm-specific antibodies can inhibit fertilization *in vitro* and animal testing in males and females of several species shows the contraceptive potential of these sperm targets (Naz 2005). Furthermore, semen from a high proportion of infertile men contains anti-sperm auto-antibodies (ASA) that block sperm functions. Examples of ASAs include FA-1 (fertility antigen-1) and YLP12 (a sperm surface epitope).

Sperm antigens identified over the last 20 years include the surface protein PH-30 (Hardy et al. 1997), and the acrosome proteins SP-10 (Kurth et al. 1997) and SP-17 (Lea et al. 1998). Partial to no contraceptive effect was demonstrated with these targets in vaccinated animals despite the ability of antibodies against these molecules to block sperm binding *in vitro*. An exciting prospect is hyaluronidase protein (PH-20), which is present in sperm in the testis and luminal fluid of the epididymis, and plays multiple roles in fertilization and penetration of the ZP coat on an oöcyte. PH-20 purified from guinea pigs was 100 % effective in male and female guinea pigs for 6-12 months following 2 immunizations with Freund's adjuvants (complete and incomplete). The contraceptive effect was reversible and correlated with the presence of specific antibodies (Primakoff et al. 1988). Unfortunately, immunization of rabbits and mice (Pomering et al. 2002, Hardy et al. 2004) with the homologous PH-20 antigen produced by recombinant means failed to induce contraception. Antigen designs that rely on chemical synthesis of the appropriate peptides or the production of recombinant proteins that resemble more closely the native protein may overcome the shortcomings of this vaccine, but this remains to be tested.

Another sperm protein that was successfully tested in female rabbits, mice, and baboons is the sperm-specific lactate dehydrogenase (LDH-C4). LDH-C4 controls lactate metabolism and glycolysis of mature spermatozoa. Vaccination with the purified LDH-C4 reduced fertility in baboons by 70 % (Goldberg 1981). A synthetic peptide antigen based on LDH-C4 was later identified and successfully tested in female baboons and rabbits in which partial contraception (up to 75 %) was achieved for one year following 4 immunizations. The contraceptive effect was completely reversible, but was reportedly caused by a cellular response rather than an antibody response to the vaccine (O'Hern et al. 1995, 1997). More recently, an LDH-C4 based DNA vaccine was tested in female mice in which the pregnancy rate remained unchanged, but litter sizes were significantly reduced (Shi et al.2005). Based on these observations, LDH-C4 may be a useful target for immunocontraception but is most likely to be used as a component of a multi-target vaccine because of its only partial effect.

FA-1 and YLP12, mentioned above, are additional sperm targets that have been used in experimental contraceptive vaccines with partial success. Antibodies to both of these sperm proteins have been detected in infertile men (Menge et al. 1999, Naz and Chauhan 2001). Furthermore, antibodies specific to FA-1 have been detected in infertile women and are believed to affect sperm function (Naz and Chauhan 2001). Efficacy of the recombinant FA-1 vaccine was short lived (3 months) and fertility was restored once antibody levels reached basal levels (by 9 months post-immunization) (Naz and Zhu 1998). This demonstrated that FA-1 is a potential target for a contraceptive vaccine in females, and that the effect is fully reversible. Unfortunately, the short duration of the response, even when potent adjuvants were used, and the partial effect exhibited by the vaccine, clearly showed that FA-1 alone cannot induce effective contraception.

YLP-12, similar to FA-1, is present on the surface of sperm and anti-YLP12 antibodies have been detected in sera and seminal plasma of ASA-positive immunoinfertile men (Naz and Chauhan 2001). To test the contraceptive potential of YLP12, the peptide was chemically synthesized and formulated in a vaccine by conjugation to a cholera toxin subunit carrier/adjuvant. Breeding female mice vaccinated with four doses resulted in a 70 % reduction of pups born 3-4 months post vaccination. The same mice produced normal litter sizes when bred 10 months following the first vaccination, demonstrating that fertility was completely restored (Naz and Chauhan 2002). Like FA-1, YLP12 required too many immunizations and was ultimately ineffective beyond the short term. It is more likely to be used in a multivalent anti-fertility vaccine targeting sperm and even then, its long-term efficacy is doubtful.

Recently, the testis-specific Eppin was explored as a target for immunological control of male fertility. Eppin, a protein found in seminal fluid, contains antimicrobial activity and binds to spermatozoa to facilitate fertilization following ejaculation (Wang et al. 2005). Unlike other sperm targets, Eppin was used to immunize males rather than females in the hope of controlling fertility in the male specifically. Macaque monkeys were immunized repeatedly (every 3 weeks) with recombinant Eppin formulated in Freund’s complete and incomplete adjuvants (O’Rand et al. 2004). Seven of 9 immunized monkeys generated antibodies against Eppin and remained infertile as long as immunizations were maintained. Unfortunately, when treatment was stopped and antibody levels disappeared, only 5 of the 7 responders regained fertility, demonstrating that a continuous immune response to the testis can cause irreversible damage, and therefore sterility, in some subjects. In conclusion, Eppin is unlikely to be a successful candidate for future contraceptive vaccines because of the extremely low immunogenicity of this self antigen and the potential irreversible sterility in the male.

Sperm antigens offer the exciting possibility that contraception can be achieved in a female by vaccination against proteins that affect sperm functions, hence “protecting” the female from the fertilization potential of sperm. Since sperm antigens are specific to males, the risk of auto-immune reactions and deleterious effects in vaccinated females is significantly reduced. Unfortunately, all sperm targets described to date share three characteristics: 1) they are weakly immunogenic and require the use of unsafe adjuvants, 2) they are only partially effective in vaccines as they affect one of many aspects of sperm function, and 3) their contraceptive effect is short lived and can be sustained only with continuous immunizations. Identification of novel sperm targets and many years of research will be needed before effective vaccines based on sperm proteins become a reality for population control.

Zona Pellucida (ZP)

The zona pellucida (ZP) is a glycoprotein extracellular matrix that surrounds mammalian oöcytes. It is composed primarily of 3 glycoproteins, ZP1, ZP2, and ZP3. An additional member of the ZP family, ZP4 was recently identified and described (Lefrieve et al. 2004, Hoodbhoy et al. 2005). The ZP armor, which protects the oöcyte and zygote until implantation, plays a critical role in sperm binding and induction of the acrosome reaction. The sugar moieties on the ZP confer species-specificity to sperm binding. The antibodies raised by the female in response to the pZP bind to her own ZP and prevent fertilization by sperm. The presence of the ZP coat until the pre-implanted blastocyst stage also suggests that anti-ZP antibodies could induce contraception by preventing embryo implantation. ZP-based vaccines have been tested in over 100 species with a good degree of success in many, but reversibility has been variable.

Historically, native ZP has been purified from pig ovaries (pZP) because of the availability of the tissue from abattoirs. Early studies with native porcine ZP in rabbits, dogs, and monkeys resulted in contraception that was attributed to disruption of folliculogenesis rather than a block in fertilization (Skinner et al. 1984, Mahi-Brown et al. 1982, Gulyas et al. 1983). In these cases, the effect was irreversible due the profound damage to the ovaries. This effect was initially attributed to impurities in ZP preparations. However, when a purified mixture of porcine ZP3 was subsequently tested in female squirrel monkeys (Sacco et al. 1987), macaque monkeys (Bagavant et al. 1994), and dogs (Mahi-Brown et al. 1985), adverse effects on follicular development and ovarian function were demonstrated for squirrel monkeys and dogs. Macaque monkeys, on the other hand, had normal ovaries and cycled properly. The improved purification of ZP components has lessened the damaging effect of the vaccine on the ovaries, but at least in some species, the contraceptive effect was still attributed to ovarian dysfunction. Interestingly, when macaque monkeys were immunized with purified ZP3 and Freund's complete adjuvant (Upadhyay et al. 1989), ovarian follicular atrophy was reported, which was attributed to the high antibody titers generated by vaccination with the potent adjuvant.

The level and quality of anti-ZP antibodies generated by various vaccine technologies can have profound effects on blocking fertilization and causing irreversible ovarian damage. Long-lasting antibodies are desired to block sperm function and/or prevent implantation of the embryo, but persistent antibody levels that are present at a high level may profoundly affect ovarian function and therefore induce sterility. Further support for this mechanism comes from dogs that were immunosterilized, rather than immunocontracepted, by vaccination with ZP also had the highest anti-ZP titers (Fayrer-Hosken et al. 2000).

Numerous studies with recombinant ZP proteins and ZP-based peptides have revealed that the ovarian pathology observed in some species as a result of ZP vaccination is mediated by immune responses targeting specific part of the ZP rather than the presence of contaminating proteins. Although irreversible ovarian pathology has been occasionally observed in animals immunized with recombinant ZP1, ZP2, or ZP3 (Paterson et al. 1998, Kerr et al. 1999, VandeVoort et al. 1995, Govind et al. 2002), it is believed that immunizations with ZP3, in particular, are associated with ovarian atrophy. Multiple immunizations with recombinant ZP1 (5-8 immunizations) conferred reversible contraception in monkeys, (Martinez and Harris 2000). Immunizations with recombinant ZP2 (rec75) and ZP1 (rec55) revealed that ZP2 causes ovarian pathology whereas ZP1 does not (VandeVoort et al. 1995).

Epitopes of ZP2, ZP1, and ZP3 that are devoid of damaging oöphoritogenic potential have been identified (reviewed in Naz 2005). Tests of these peptide antigens, either alone or in combinations, resulted in some degree of contraception in various species. More importantly, the peptides did not cause damage to the ovaries. Unfortunately, the antigenicity of the peptide antigens is weak, which may explain the limited efficacy in breeding trials. To improve the efficacy of the peptide antigens, it has been proposed that combinations of multiple ZP epitopes may be more effective in a vaccine. In agreement with this, a mixture of ZP peptide antigens or a long synthetic peptide encompassing multiple peptides were more effective than the individual peptides in blocking sperm binding *in vitro*. (Afzalpurkar and Gupta 1997, Sivapurapu et al. 2005). The effect of these peptides on fertility *in vivo,* however, is unknown. In a similar study, antibodies raised against a mixture of ZP peptide antigens significantly reduced *in vitro* fertilization but had no contraceptive effect in marmosets (Paterson et al. 2000). Clearly, research in the area of ZP-based peptide antigens is progressing and epitopes with contraceptive potential that do not cause ovarian pathology are being identified, but considerable research is still needed to identify combinations of ZP epitopes that will produce antibodies capable of inducing infertility *in vivo*.

What is the potential for a ZP-based contraceptive vaccine for the control of wildlife? The research on recombinant forms and synthetic peptides of ZP will be instrumental for the mass production of ZP antigens in a controlled reproducible form that will be favored by regulatory agencies. This, however, is still a distant goal particularly since such antigens are not consistently efficacious. Multiple immunizations (typically greater than 3) with such antigens are required to induce high antibody levels and the contraceptive effect is only partial. For now, the only effective alternative is purified porcine ZP, which can induce contraception in several species after repeated injections. In elephants, for example, a partial contraceptive effect (10 out of 19 and 8 out 18 were infertile) was observed after three immunizations in two studies (Fayrer-Hosken et al. 1999, Delsink et al. 2002). In deer, three immunizations with the potent Freund’s adjuvant conferred partial contraception in the first year, and three additional immunizations were required for a complete arrest of fertility in the second year (Miller et al. 2000). The only ZP-based vaccine capable of inducing multi-year contraception with a single immunization is SpayVac®, a vaccine consisting of purified porcine ZP in a liposome formulation. SpayVac® proved effective for at least 10 years in seals (Brown et al. 1997, R. Brown pers. comm.), and 3 years in deer (Fraker et al. 2002).

A conventional pZP vaccine has also been tested on captive black bears by Dr I. Liu (pers. comm.). It was 100 % effective in a 2-year trial using 22 pZP-treated sows and 5 sham-treated sows. The vaccine used the adjuvant QA-21, with the booster contained in slow-release pellets, which were administered simultaneously with the primary dose. The vaccine would require boosters to maintain long-term contraception. The Humane Society of the US is currently conducting experiments with captive bears using a pZP vaccine. These experiments, which began in November 2004, used a pZP vaccine with Modified Freund’s Adjuvant (MFA) in the primary dose, and a booster dose contained in slow-release pellets, which incorporated the adjuvant QA-21. Results in the first year were that both control sows both gave birth, while 1 of 3 pZP-treated sows gave birth (A. Rutberg, pers. comm.). Given that conventional pZP vaccines can be effective in black bears, SpayVac® would likely to be effective for several years in bears, as it has been in other species. However, SpayVac® does not have regulatory approval and the current INAD (Investigational New Animal Drug) exemption applies only to deer.

Contraceptive Chemicals

Hormone-based contraceptives

Development of hormone contraceptive formulations for males and females stems from the need to control fertility in humans. The "pill" currently marketed for women is not new and must be taken orally every day. To eliminate the need for daily intake of oral contraceptives, slow release formulations marketed as a 1-week patch containing norelgestromin (a synthetic progesterone) and ethinyl estradiol (a synthetic estrogen) or a 3-week vaginal ring containing etonogestrel (another synthetic progesterone) ethinyl estradiol were introduced. A longer acting contraceptive alternative, depot medroxyprogesterone acetate (DMPA, Depo-Provera®), is currently available as an injectable formulation that is administered every 3 months in women. Although DMPA is generally regarded as safe, potential side effects are abnormal endometrial bleeding, and more importantly, reversible bone density loss that results from prolonged suppression of ovarian estradiol production. Bone density is regained following discontinuation of DMPA.

Longer-lasting hormone implants containing a progestogen have been developed and marketed in numerous countries including the USA. The early generation implants, notably Norplant® (6 levonorgestrel capsules every 5 years) and Jadelle® (2 levonorgestrel rods every 5 years) were difficult to implant and caused irregular bleeding patterns, a common side effect of progestogen-only contraceptives. A newer implant, Implanon® (one flexible rod every 3 years), is currently marketed in Australia and the EU, with approval pending in the USA. Implanon®, containing the progestogen etonogestrel, provides contraception by suppressing the LH surge and increasing the viscosity of cervical mucus which effectively reduces sperm motility. Implanon® is favored over other implants because of the ease of implantation and removal. While vaginal bleeding is reportedly lower with Implanon® than with Norplant® (Meckstroth and Darney 2001), considerable disturbances of menstrual patterns have been reported by 10-20 % of users. These include amenorrhoea (absence of menstrual period) or frequent / prolonged bleeding. Other side effects, including headache, weight change, and acne, were problematic in less than 5 % of users. In general, no severe adverse events are associated with the use of implants.

A two-year implant containing the synthetic progestogen, Nestorone® (Elcometrine™), is under development by Population Council researchers (Sivin and Moo-Young 2002). The use of Nestorone is potentially more applicable to wildlife population control than Etonorgestrel because this hormone is inactive when ingested orally. In a recent clinical trial in 300 women, Nestorone® caused menstrual and medical (headache, weight gain) disturbances which accounted for 33% of discontinuation of Nestorone® in the two-year trial (Sivin et al. 2004). The side effects of a Nestorone implant in bears are unknown and would have to be examined. The reversibility and the inactivity of the hormone following ingestion will ultimately be advantages for the possible widespread use of Nestorone®-like hormone implants for animal population control as long as the side effects, if there are any in the target species, are considered acceptable.

Currently, there are no approved hormone contraceptives for males, but research in this area is active. Repeated administration of sex hormones causes negative feedback to the hypothalamus-pituitary axis, which suppresses LH and FSH production. This results in azoöspermia (total loss of sperm) and decreased testosterone production. Early studies conducted in the 1970s clearly showed the reversible contraceptive potential of testosterone when administered continuously. Testosterone served two purposes: it blocked pituitary functions and provided replacement of endogenous testosterone that was no longer produced. A large WHO-sponsored study with weekly intramuscular injections of testosterone enanthate (WHO 1996) induced partial contraception, which was attributed to oligospermia (reduction in sperm) rather than azoöspermia. Testosterone alone was unable to induce reproducible infertility in all men, which prompted experimentation with progestogen / testosterone combinations as an alternative. More recently, a number of small studies in men examined the use of progestogens (etonogestrel, desogestrel, or levonorgestrel) to induce infertility in conjunction with "add back" testosterone to alleviate the symptoms associated with testosterone loss (reviewed in Grimes et al. 2004). Many of the studies described used progestogen implants to induce long-term infertility, but testosterone (or its derivatives) was administered routinely. While the progestogen / testosterone regimen is preferred over other hormonal approaches, the observed efficacy varied from 0-100 %. Testosterone derivatives, such as 7 alpha-methyl-19-nortestosterone (MENT) (Von Eckardstein et al. 2003), that can be placed in long-term implants to complement the effect of progestogens need to be identified and tested. To date, no reliable, long-term hormone contraceptive for males has been developed.

As an alternative to hormones, GnRH agonists and antagonists have been explored as potential contraceptives. GnRH agonists and antagonists are chemically synthesized homologues of the GnRH decapeptide. Agonists are chemically modified to increase the half-life of GnRH in the circulation and are considerably easier (and cheaper) to synthesize than the antagonists, which contain complex modifications that allow binding to GnRH receptors without activating them. Agonists continuously stimulate GnRH receptors, which causes their down-regulation. Immediately following administration of agonists, an acute phase with increased LH and FSH secretion precedes down-regulation of the gonadotropins. The surge usually induces undesirable estrus in females, as was evident in a number of animal models including cats and dogs (Herbert and Trigg 2005). Since the surge is transient (1-2 weeks), it is unlikely to have a significant effect in males. Early trials with agonists in human males were not very effective in suppressing spermatogenesis, most likely a result of unsuccessful FSH down-regulation (Wang 2004). However, recent studies with a long-term GnRH agonist implant (Suprelorin®) containing the agonist deslorelin, showed that it can effectively control fertility in male dogs in the short term. The use of Suprelorin® in male dogs has been approved in Australia with efficacy duration of 6 months. Suprelorin® implants have been tested in females of various species, including wallabies, cows, cheetahs, cats, and dogs. Treatment with the agonist induced premature estrus in a high proportion of females regardless of the species tested and efficacy varied from 83 % to 100 % for periods ranging from 70 days to 640 days post-implantation (reviewed in Herbert and Trigg 2005). Duration of infertility was highly variable among species as well as individuals within a species. Research is currently aimed at developing a longer acting deslorelin implant with a target duration of 12 months.

GnRH antagonists induce infertility by interfering with the interaction between circulating GnRH and GnRH receptors. Antagonists (e.g., acyline, Cetrorelix®, Teverolix®, and Ganirelix®) block signaling through the receptor, effectively stopping downstream events such as LH and FSH secretion, and hence spermatogenesis and follicular development. Unlike GnRH agonist analogs, antagonists do not cause LH / FSH surges. In early studies with antagonists, injection-site reactions and histamine-like allergic reaction were observed and almost halted research in this area. Fortunately, antagonists with good safety profiles have been identified (reviewed in Merviel et al. 2005). Although GnRH antagonists show promise and may be more effective than agonists, they have to be administered routinely to maintain efficacy. Considering the high cost associated with the production of antagonists, and the lack of long-term slow-release formulations, it is unlikely that antagonists will be used for the control of animal populations in the near future.

Neutersol®

Neutersol® is the first FDA-approved, non-surgical sterilization treatment for male puppies 3-10 months of age (Technology Transfer Inc., 2003). Neutersol® consists of a one-time injection of zinc gluconate in each testicle, effectively causing "severe atrophy of the testicles…and partial atrophy of the prostate glands," and abolishing sperm production. Testosterone levels were reduced by 41 %-52 % over the 24-months trial, although at month 24, 70 % of the treated dogs had levels that fell within the control range. As the only FDA-approved non-surgical alternative to castration for animals, Neutersol® is endorsed by the American Humane Association, the Humane Society of the United States, the American Society for the Prevention of Cruelty to Animals, and the American Veterinary Medical Association. The use of Neutersol® for chemical sterilization of species other than dogs is permitted under provision of the Animal Medicinal Drug Use Clarification Act (AMDUCA). Neutersol®'s target market is clearly young companion animals whose owners are seeking an alternative to surgical castration. In dogs, the reduction in testicle size ranges from 25 % to 75 %, with the largest reduction observed in dogs treated as younger puppies.

Intrauterine Devices

Intrauterine devices have been used in horses and ponies, and presumably could be used in bears as well. G. Killian et al. (2004) tested copper "T" IUDs, designed for humans, in wild horses and ponies, but found a high failure rate. Large marbles (3.5 cm) have also been used in horses but were <50 % effective (Nie et al. 2001). The marbles have the additional benefit of inducing pseudopregnancy, although the mechanism is not understood. IUDs that have been approved for use in humans might also work in bears. Efficacy will probably depend on how well the devices fit. Presumably, IUDs would have to be replaced every 3-5 years, as they are in humans. Determining whether IUDs would have any application in black bear contraception would require trials with captive bears.

Surgical Procedures

Vasectomy in males and tubal ligation in females have been used experimentally on a limited scale in other wildlife species. Veterinary support and appropriate equipment is needed to conduct these surgeries under field conditions. Past experience with white-tailed deer near Ithaca, NY, has shown that it is difficult and expensive to maintain veterinary and anesthesiology staff on call for wildlife capture at remote sites during early mornings or late evenings when a large proportion of wildlife captures are made (P. Curtis, pers. obs.). Some communities have used donated ambulances to establish a mobile surgical suite with the necessary equipment to treat deer. This assumes that there is reasonable road access into areas where animals are captured. Bears would need to be monitored for several hours post-surgery to ensure that recovery is complete. The surgical team would need to develop specific expertise with sterilizing bears, as this is not typically included in training for veterinarians. Even surgical procedures are not always successful: 3 of 22 white-tailed deer females surgically "sterilized" near Ithaca, NY, became pregnant within two breeding seasons after their operation (P. Curtis, unpubl. data). There is always risk of post-surgery complications and the potential for infection and mortality.

Contragestational Agents

Toward the end of pregnancy, the corpus luteum (CL) regresses in response to prostaglandins, particularly $PGF_{2\alpha}$, resulting in a precipitous drop in circulating progesterone (Nalbandov 1976). Prostaglandins (e.g., Lutalyse®) are used routinely in the cattle industry to synchronize estrus and induce parturition (Lauderdale 1972) and are approved for use in food animals. DeNicola et al. (1997) used $PGF_{2\alpha}$ to terminate pregnancy in white-tailed deer.

N. Call (pers. comm.) uses Lutalyse® to terminate black bear pregnancies at a large bear facility. The protocol is 2 inoculations of 2 mL, one given after the breeding season in late August or early September and the other given in late October. This is during the embryonic diapause (delay phase), prior to implantation. Whether 2 inoculations are necessary is not known. The procedure is approximately 90 % effective.

$PGF_{2\alpha}$ is effective only after breeding and must be administered every year.

Conclusions

Contraceptives that can be applied successfully to managing wildlife population size must have certain attributes. The most important of these are:

1. Single-dose and long-lasting (i.e., multi-year; capturing individual bears is difficult and expensive, and they may not be easily recaptured).
2. Must not introduce harmful chemicals (e.g., synthetic hormones) into the food chain where they could affect predators, scavengers, or humans.
3. Must not adversely affect social behavior of treated animals.

For males there are 2 options available for sterilization: Neutersol®, a chemical sterilant, and vasectomy. Neutersol® is approved for use in dogs and is being tested presently on captive bears (G. Stull, pers. comm.). If injected at an appropriate dose, this will undoubtedly result in sterilization. However, the resulting damage to the testes and lowered testosterone production will almost certainly relegate treated animals to subordinate social status. Male sterilization cannot be effective on a population level unless nearly all males are treated. Vasectomy will sterilize males with no adverse effects on testosterone levels, although the procedure involves a risk of infection and few veterinarians have the required experience on bears to perform the surgery. (Castration might also be used, but this would render the animals completely asexual.)

Approaches for females include vaccine-based and chemical-based contraceptives. Long-lasting hormone contraceptive implants, such as etonorgestrel are soon to be approved in the USA for women and would surely be effective in any mammal including bears. However, there are concerns about the use of synthetic hormones, which do not degrade readily and can be transferred through the food chain. Until a biodegradable hormone contraceptive devoid of significant side effects is developed, the use of hormone implants is unlikely to be approved by wildlife management authorities.

Another chemical-based approach is Lutalyse®, a contragestational preparation which works well on bears and has regulatory approval. Unfortunately, Lutlyse® would have to be administered annually after the breeding season, either just before or during denning. The required timing of the administration of Lutalyse® would increase both the technical difficulties and cost.

Currently, contraceptive vaccines are generally recognized as the only effective and practical non-lethal means for controlling wildlife fertility, although none has regulatory approval. For applications to wildlife population management, the need is for a long-lasting, single-dose vaccine. Immunocontraceptives that may be effective in bears are currently limited to those based on GnRH and pZP antigens.

GnRH is the only hormone that can be used safely in a vaccine and is effective in the short term with a minimum of one dose. GnRH vaccines can be applied to both males and females, but it will be most effective in population control if used in females. The ability to synthesize GnRH chemically would facilitate the manufacture and regulatory acceptance of this antigen. The use of GnRH in a single-dose regime may be effective in some species, but the current literature suggests that the efficacy period may be as short as 3-6 months post-vaccination. A strategy of immunizing animals 3 months before the start of a breeding season may effectively reduce the fertility of the animals until the following breeding season, but an annual vaccination program would be necessary.

GonaCon™, a GnRH vaccine developed by the USDA-National Wildlife Research Center, is a safe GnRH formulation that shows short-term efficacy with a single dose in male cats (Levy et al. 2004). Published data on GonaCon™ and other GnRH-based vaccines, however, suggest that a single-dose long-lasting (multi-year) efficacy is unlikely to be achieved with the current design of GnRH vaccines. The basic problem is that the immune response to the GnRH-KLH conjugate is largely due to the more antigenic KLH component, which is irrelevant to the reproductive system. Over time and with repeated boosters, carrier-mediated suppression occurs whereby anti-KLH antibody levels are maintained but fewer antibodies that recognize GnRH are produced. This is quite acceptable where the need is short term, as it is for pigs and cattle, but not for wildlife. GonaCon™ is presently being tested in deer and horses, and no results are yet available in the peer-reviewed literature. However, Ragonese (2006) reported preliminary results about performance in deer that were not encouraging. In a 1-year study in New Jersey, the failure rate was 30 %, while in a Maryland study, there was a 12 percent failure rate in year 1, increasing to 53 % in year 2.

Of the existing FC agents, pZP vaccines are the most promising. The extensive experience in deer, horses, and other species indicates that they are effective without having significant adverse effects on behavior and social structure. Most pZP vaccines require booster immunizations to be effective, but a single dose of SpayVac® has proven effective over several years in many species including deer, seals, and horses.

A possible concern with pZP-based vaccines is their potential to induce irreversible infertility, although the general health of pZP-sterilized females is not affected. Current knowledge suggests that the degree of ovarian dysfunction is species-specific, and the reversibility of a long-lasting pZP vaccine in bears would have to be determined. The single-dose pZP vaccine, SpayVac®, caused long-term infertility in seals (longer than 10 years), most likely a result of long-lasting antibody responses rather than damage to the ovaries. Histological examination of ovaries from seals 5 years following vaccination with SpayVac® showed no ovarian abnormalities (R. Brown, pers. comm.).

5 CAPTURE TECHNIQUES

Cable restraints are often used for capturing free-ranging black bears. Restraints are made from 3/16" aircraft cable, fitted with a car-hood spring and swivel (Johnson and Pelton 1980), and anchored to trees ≥12" diameter breast height (DBH). A 4-m radius around the tree is cleared of all brush to prevent bear entanglement and possible injury. Traps are usually baited (e.g., lunch meat, bacon, pastries, road-killed deer, or fish), and are checked once daily, usually in the morning (Telesco 2003; Dobey 2002). If temperatures are forecast to reach 32° C, traps are usually inactivated during mid-day (Telesco 2003).

Captured bears are often immobilized with a mixture of two parts ketamine hydrochloride to one part xylazine hydrochloride (Horner and Powell 1990). Dosage rates are 8.8 mg/kg ketamine hydrochloride and 4.4 mg/kg xylazine hydrochloride (Thompson 2003) based on estimated weight. Immobilization drugs may be administered by jab-stick, blowgun, or dart rifle. Teletamine hydrochloride/zolazepam (Telazol) is a suitable drug alternative (Taylor et al. 1989). Telazol is particularly useful for winter bear capture because bears do not suffer respiratory depression and are able to thermoregulate while immobilized (Haigh et al. 1985).

Pulse rate, breathing rate, and temperature should be monitored from immediately after immobilization until recovery. If the bear's estimated age is 1.5 years or more, a first upper premolar should be removed for aging (Willey 1974). Body measurements and weight should be recorded. Yohimbine hydrochloride may be given to reverse the effects of the xylazine hydrochloride and speed bear recovery.

In areas with thick brush or small-diameter trees, culvert traps may be used to capture bears. These traps are very useful in late spring and early summer when food sources are more limited. Good road access is needed to transport these large, heavy traps. This technique may be more appealing and safer in suburban locations because the bear is contained within the trap, and the trap can be marked with large warning signs.

Capture may also occur during winter at bear dens. This is usually feasible only for bears previously caught and fitted with radio collars. Den sites may be found by homing in on the signal from the radio collar, and den visits are often scheduled for early- to mid-March. This is an excellent time to determine if female bears were pregnant, and if so, take data on cubs.

Trained and licensed dogs may also be used to tree and capture nuisance bears. This technique is more suited to rural forest lands than to suburban situations. A bear may cross many properties and be treed in an area where the landowner refuses to provide access. If the technique can be used, bears are typically immobilized with a dart rifle while in the tree, using the drug combination described previously. Ropes and ladders may be necessary to lower the bear from the tree.

The capture and handling of bears is expensive. Current capture cost incurred by the New Jersey Division of Fish and Wildlife is $>1000 / bear (FGC 2005). Because current research staff do not intend to capture all or even most of the bears in a particular area, the bears that are being captured presently are the most vulnerable. If there were an intention to capture a large proportion of the bears in an area, the costs / bear would increase significantly as more time and effort are needed to catch trap-shy individuals. Different age and sex classes of bears may be more vulnerable to trapping than others. For example, it may be easier to capture juvenile bears than adults. Because of their large home ranges and wariness, adult male bears may be the most difficult animals to capture.

If natural foods are plentiful, even an experienced trapper may catch only a small proportion of the bears using an area. Bears often prefer to forage on natural foods (e.g., berries, acorns, etc.) if they are abundant. It would be anticipated that the proportion of bears caught in an area would be higher during drought years when natural foods are less plentiful. There is an apparent correlation between drought years and high levels of nuisance complaints (Peine 2001).

Recapturing bears may be problematic. Trapping or snaring bears is a highly aversive experience for many individuals and can be used as a technique to train bears to avoid humans, residential areas, and buildings. Bears that are captured can be fitted with radio collars, which enable subsequent recapture during the wintering denning period.

6 REGULATORY FRAMEWORK

Vaccines and other drugs "… intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals … or intended to affect the structure or function of the body of man or other animals … ." are regulated by the Food and Drug Administration (FDA) under the Federal Food, Drug and Cosmetic Act (Fagerstone et al. 2002). Veterinary products that are "… intended for use in the diagnosis, treatment, or prevention of diseases in animals," are regulated under the Virus, Serum, Toxin Act by the Animal and Plant Health Inspection Service (APHIS) of the US Department of Agriculture. Because pregnancy is not a disease, contraceptive products fall under the FDA, rather than APHIS. [NOTE ADDED IN PROOF: In 2006, regulatory authority for contraception of wildlife and feral animals was transferred from the FDA to the EPA (Environmental Protection Agency). The implications of this change are not known at present.]

There are no contraceptives that are specifically approved for bears or any other wildlife species. However, under provisions of the Animal Medicinal Drug Use Clarification Act (AMDUCA), with a few exceptions, products approved for one species can be prescribed for use in another at the discretion of a licensed veterinarian. For example, Neutersol®, which is approved for use in dogs, could be legally used on bears. This is often referred to as "extra-label" use because the application is outside the guidance on the FDA-approved label and other information that accompanies the product. Because of the very high cost of meeting regulatory requirements and the very small size of the wildlife-applications market, there are no drugs approved specifically for a wildlife species. Nevertheless, drugs used on domestic species are routinely used on wildlife. For example, Telazol®, approved for use in dogs and cats, is routinely used to immobilize bears (Haigh et al. 1985).

Products that are not approved for any species may be used experimentally under the authority of an Investigational New Animal Drug (INAD) exemption issued by the FDA. This exempts the new animal drug from the prohibition on interstate transport of unapproved products. Unapproved drugs can be used on captive animals without an INAD, but use on free-ranging animals requires an INAD. For example, PZP vaccines, none of which are approved for use on any species, would require an INAD specifically for bears. Because the granting of an INAD requires a credible plan leading to commercialization of a new drug, it is not clear that an INAD would be issued for a drug specifically intended for use on bears. The cost of meeting the requirements for regulatory approval may be high – in the range of several million dollars – and are very unlikely to be justifiable to any potential funding entity. In addition, it is difficult to conceive of where one might find an adequate number of bears on which to conduct statistically valid trials to determine efficacy and target-animal safety.

7 EVALUATION OF FERTILITY CONTROL

To manage the size of a given population using fertility control, an effective agent is required. However, it is just as important to have a means of delivering that agent to a sufficiently large proportion of the population. The ideal contraceptive agent should possess the following attributes:

- Safe and effective for the treated animals
- No adverse effects on social relations of the treated animals
- Is effective on females
- Has regulatory approval
- Has no adverse effects on the food chain (including humans)
- Does not require repeated treatments
- Does not require skills beyond those possessed by most wildlife biologists or technicians
- Reasonable costs for materials and delivery

Effectiveness of Selected Fertility-Control Agents

Table 2 summarizes our assessment of various fertility-control agents. Because of the impracticality of applying male-oriented contraception for population control, efficacy is rated for females only. Practicality relates to special requirements that would be problematic. For example, surgical sterilization would require a veterinarian and might require transporting the animal to a clinic. Surgical sterilizations applied on any sort of scale intended to achieve population control would be impractical. Practicality also encompasses whether repeated treatments are necessary. Cost primarily is a function of the labor involved. If animals have to be recaptured, costs increase greatly. Effects on individual bears relate to the intended consequences of the treatment, and not complications that might ensue, for example, from post-operative infection after a surgical procedure.

The FC strategy must target females to be effective. This is a consequence of 4 biological realities. First, it is the females that become pregnant and produce the young. Second, because a single male can inseminate a large number of female black bears, virtually every male would have to be effectively treated to reduce the production of young; treating even 80 – 90 % of the males might have little or no effect on the number of offspring produced. Third, females tend to reside in relatively restricted areas for their entire lives, at least during spring and the breeding season, while males travel over much larger areas. This means that to control the number of young produced by the females in a particular area, the males in a much larger area would have to be treated. And fourth, males disperse over large distances. For male contraception to be effective, constant vigilance would be required to detect and treat new males that enter the management area. Targeting males in an FC program simply cannot be effective.

Table 2. Summary of evaluation of fertility-control agents for application to black bears. 1 = most favorable, 2 = moderately favorable, 3 = less favorable, 4 = unfavorable, NA = not applicable, U = unknown. Where direct evidence from bears is not available, the assessment is based on information from other species.

Fertility-control Agent	Efficacy on Females	Duration of Efficacy[a]	Regulatory Approval	Food Chain Concerns	Effect on Social Structure	Effect on Individual Bears	Practicality	Cost
PZP	1	3	U	1	1	2	3	3
SpayVac® – PZP	1	1	U	1	1	2	2	2
GnRH	1	3	U	1	U	2	3	3
Hormone implants	1	3	4	4	1	2	3	3
Injectable Hormones	1	3	4	4	1	2	4	3
Neutersol®	NA	1	1	1	3	3	NA	3
Vasectomy	NA	1	1	1	1	1	4	4
Tubal ligation	1	1	1	1	1	1	4	4
IUD	U	U	U	1	2	2	U	U

[a] 1 = >5 years, 2 = 2-4 years, 3 = 1 year, 4 = <1 year

Of the fertility-control agents described in the previous section, pZP vaccines, which are administered to females, have been used for >25 years in a number of species and are generally regarded as safe (Kirkpatrick et al. 1997). Such vaccines have proven effective on bears (I. Liu, pers. comm.), and trials of a similar pZP vaccine are currently underway on captive bears in New Jersey (A. Rutberg, pers. comm.). Overall, pZP vaccines score high in the rating for potential use on bears. The main limitation of most pZP vaccines is the short duration of efficacy. Although this is not known at present for the pZP currently being tested in New Jersey, it is likely that boosters will have to be administered every year or two to maintain contraceptive antibody titers. The administration of boosters could be facilitated if the bears were fitted with radio-collars when first captured, which would allow the bears to be located in their dens during winter. It is uncertain whether the regulatory authorities would permit field trials of an experimental pZP vaccine, including SpayVac®.

SpayVac® is a long-lasting, single-dose pZP vaccine that has proven to be highly effective in several species (e.g., white-tailed deer, fallow deer, horses) in which conventional pZP vaccines have also been effective (Fraker et al. 2002, R. Brown pers. comm.). Given that a conventional pZP vaccine has proven effective in black bears, it is likely that SpayVac® will also perform well in this species. However, the manufacturer of

SpayVac®, ImmunoVaccine Technologies, Inc., is presently unwilling to become involved in any trial on bears (W. Kimmins, pers. comm.).

Neutersol®, a sterilant that is approved for use in male dogs, has been proposed for use in bears by Millenium Wildlife Sciences (G. Stull, pers. comm.). Trials are underway at present to test Neutersol® on male black bears, so the effects are not yet known with certainty. However, in dogs, Neutersol® results in reduced testosterone levels and "severe testicular atrophy" (Technology Transfer 2003), and we would expect the same outcome in bears. Because dominant males do most of the breeding in black bear populations (Kovach and Powell 2003) and such males have high testosterone levels (Garshelis and Hellgren 1994), we suspect that Neutersol®-treated bears would be relegated to subordinate status. In addition, capture efforts would have to be maintained each year to detect, catch, and treat immigrant males *before* they could mate with females. It is inconceivable that a large enough proportion of the males could be captured and treated for this approach to be effective. (Although vasectomized bears would still maintain normal testosterone levels and would actively participate in mating, the fatal flaws in attempting to achieve population control by treating males still remain.)

G. Stull (pers. comm.) also suggests that sterilized dominant males, assuming that high testosterone levels and dominance status remain unchanged, would mate exclusively with most of the females in the population and as a consequence of coitus, these females would exhibit pseudopregnancy. As discussed in the Reproductive Biology section, pseudopregnancy in bears does not occur until well after the breeding season and has no effect on breeding activity.

Prostaglandins (e.g., Lutelyse®) have been proven to work well in captive bears, but must be administered after the breeding season has concluded and before birth. Radio-collared bears could be followed to their dens every year. Lutelyse® has the advantage of already having regulatory approval for use in food animals. The obvious disadvantage is the need to treat each animal every year.

GonaCon® is a GnRH vaccine that is presently undergoing regulatory approval trials in deer. Because GnRH vaccines act early in the cascade of events in the HPG axis, where the physiology is highly conserved among species, it is very likely to be effective in many species, including bears. However, GnRH vaccines have not been tested in bears. Because these vaccines have so far not proven to be long lasting, individual bears probably would have to be treated annually to maintain contraception.

Hormone implants and injectable preparations, which mimic the hormone changes that occur during pregnancy, have been used in humans for many years. Norplant® is a well-known implant, while DepoProvera® is a well-known injectable. Implants are effective in humans for 3-5 years, while DepoProvera® is effective for just 3 months. Only the longer-lasting implants would appear to have any potential for use in wildlife. None of these has been tested in bears, so dosages would have to be determined. There is concern about the consequences for humans and scavengers who might consume bears treated with synthetic hormones.

IUDs have been tried in certain animal species, e.g., horses, but not bears. Whether any type of IUD could be effective in bears is unknown.

Potential to Administer Fertility-Control Agent to Bears

The fertility-control agents discussed above include those that could be applied to males and females. Because male and female bears behave quite differently, they need to be considered independently.

Males – Males travel more widely than do females, particularly during the breeding season. A male home range will encompass the territories of several females. Consequently, traps in a particular area will potentially capture male bears from a much larger area than they will for females. The male population is also much less stable between years; that is, there is a higher turnover, with a higher proportion of immigrants.

Females – During the breeding season, females reside in territories, which they occupy for much of their lives. The female offspring tend to settle near their mothers, sometimes taking over part of the mother's territory. To capture females during the breeding period, it would be necessary to set a trap in each territory, and this would require some knowledge of the likely size and distribution of the territories. During the late summer and fall feeding period, females and their cubs may also travel widely.

Conclusion

Although fertility control has shown considerable promise for managing certain wildlife populations, such as urban deer, attempting to manage bear populations in this manner would be very difficult and expensive, and would almost certainly fail.

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Errors are, of course, the responsibility of the authors.

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