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CONTRACEPTION IN FREE-RANGING WILDLIFE

In recent years, the concept of controlling free-ranging wildlife populations by nonlethal means, particularly through contraception, has received increasing attention. The reasons for this new emphasis on fertility control as a population management tool for free-ranging species are multiple and diverse. Some species are afforded protection by virtue of their location, in national parks or other legally designated refuges that do not permit hunting or other lethal methods such as poisoning or trapping, whereas other species, such as the North American wild horse (*Equus caballus*), have been protected through federal legislation (throughout this chapter the term wild, instead of feral, is used to identify North American free-ranging horses, to remain consistent with the Free-Roaming Wild Horse and Burro Act). White-tailed deer (*Odocoileus virginianus*) have found themselves in the protective custody of increased urbanization, in areas where hunting is no longer legal, wise, or safe, or sometimes not acceptable to the public. Finally, certain exotic species that are threatening to native flora and fauna must be controlled to protect fragile habitats and ecosystems.

In many instances, changing societal values and the resulting public opposition to lethal controls have also changed the direction of management philosophies. The general public clearly does not view wildlife management in the same manner it did 50 years ago (Herzog et al. 2001), and this trend is worldwide in scope. It is important here to make clear that these changing values are not just a function of the views and activities of animal protection groups or organized efforts to halt lethal controls, but represent a general philosophical shift in thinking by a larger public. Opposition to waterfowl hunting and the shooting of kangaroos is common in Australia, fox hunting has lost its popularity in Britain, and the culling of elephants has created a split in the attitudes of Africans.

At the same time, the application of contraception to captive exotic species has become a common and increasingly important management tool for zoo personnel and has been demonstrated to be a highly successful approach to controlling some animal populations (Seal 1991). The application of contraception to free-roaming wildlife as opposed to captive exotic species, however, introduces a variety of new problems and challenges to the field of wildlife fertility control. The first issue is that of contraceptive delivery where the animals are not confined, usually quite wary, and seldom disposed to facilitate the application of the contraceptive. This particular dimension of the problem brings form and substance to the "art" of wildlife contraception, in addition to the science of this arcane subdiscipline. A second challenge involves regulatory issues, because treated free-roaming wildlife may represent food animals for scavengers, predators, or even humans. A third issue is whether or not the particular wildlife species is perceived as "desirable" or a "pest" by the public, because that attitude in turn will dictate the specific parameters of the contraceptive, whether reversible or not reversible, that may be employed. These are only a few of the unique problems attendant to altering reproductive success in free-ranging species.

Before 1980, there are few published reports of attempts at contraception of free-ranging wildlife and even fewer successes. Since that time, an increasingly large research effort has been mounted to address the problems of wildlife fertility control, but even after more than 20 years the actual number of applications in the field, as opposed to research with controlled populations, is strikingly small and reflects the difficulties attendant on this endeavor. Thus, despite the large body of literature reflecting sound research with captive animals, this review focuses almost exclusively on published actual field applications, successful or unsuccessful. Despite the focus here on field applications, it is noteworthy that contraceptive research and application within the zoo community have made significant contributions to fertility control in free-ranging wildlife by providing captive models under controlled conditions before moving into the field. A number of studies of sterilization in various wildlife species are reported in the literature, but these are not included here because they do not, by definition, concern contraception.

A brief examination of the history of contraception in wild canids and cervids is instructive, if only to highlight some of the problems associated with actual application of fertility control in the field despite technology that showed promise in a captive setting. Several compounds were tested during the 1950s and 1960s that showed pharmacological promise for inhibiting fertility in coyotes (*Canis la-*

ans) (Baker 1964; Gates et al. 1976; Thompson 1976) and two species of foxes (Linhart 1963; Linhart and Enders 1964; Cheatum and Hansel 1967). However, when field tests were conducted, bait acceptance became a serious problem. Linhart (1964) found that bait acceptance by foxes was sporadic and that nontarget species consumed the baits. Oleyar and McGinnes (1974) discovered that gray foxes (*Urocyon cinereoargenteus*) would take baits but red foxes (*Vulpes vulpes*) would not. Although Balser (1964) showed that diethylstilbestrol (DES) would inhibit fertility in captive coyotes, when it was presented in tallow baits to wild animals it was not ingested with any regularity and was poorly absorbed from the fat-based bait (Brushman et al. 1967); thus, the reproductive season often was simply delayed.

In another study of oral delivery of DES to red foxes (Allen 1982), 50 mg DES and 125 mg tetracycline hydrochloride (TC) were incorporated into pork tallow baits coated with sugar and fed to free-ranging foxes over a 4-year period. The baits were placed once each year between February 1 and February 13. An average of 70 to 75 percent of foxes inhabiting the study area consumed at least one bait, based on TC fluorescence in mandibular bone, and there was no difference between male and female consumption. Despite the success in delivering the bait, there was no difference in fertility between control and treated groups. Thus, although captive studies showed promise, the reality of application to wild animals in the field yielded disappointing results. The only successful field study of contraception in canids, with African hunting dogs (*Lycaon pictus*), occurred recently (Bertschinger et al. 2002). In this study, the gonadotropin-releasing hormone (GnRH) antagonist deslorelin was placed in long-acting implants (Suprelorin: Peptech Animal Health) after capture.

Similar results emerged from studies with deer and elk. A number of steroid compounds were shown to be effective contraceptives in captive white-tailed deer (Harder 1971; Harder and Peterle 1974; Bell and Peterle 1975; Roughton 1979) and wapiti (*Cervus elaphus*; Greer et al. 1968). However, subsequent field tests showed that steroid implants were impractical (Levenson 1984), that bait acceptance was too unreliable in the case of oral delivery (Matschke 1977), and that often the drug had to be consumed on a daily basis to be effective (Roughton 1979). Once again, the difficulties of delivering contraceptive drugs to free-ranging wildlife negated the pharmacological successes with captive animals. The same history surrounds attempts at rodent contraception, and similar problems rendered contraception of free-roaming rodents ineffective.

Much research has been conducted in the search for new and effective contraceptive agents for wildlife (Kirkpatrick and Turner 1984, 1991; Seal 1991), but disappointingly few efforts have found their way to actual field tests or management-level applications. Unfortunately, many attempts at the development of wildlife contraceptives have occurred without much thought to the unique logistical and physiological problems associated with free-ranging animal populations. Until 1991, no attempts had even been made to hypothesize an "ideal" wildlife contraceptive. Thus, research was often aimed wide of the mark. Although some of the characteristics of such a contraceptive that emerged were arbitrary, there was some agreement that a pattern for success had been established. Before reviewing these characteristics, it is important to understand that these were constructed around the issue of North American wild horses; thus, there are some peculiarities that do not necessarily apply to other species.

The proposed ideal contraceptive for wild horses included the following characteristics: (1) contraceptive effectiveness of at least 90 percent; (2) safety when administered to pregnant females; (3) reversibility of contraceptive action; (4) relatively minor cost; (5) absence of short- or long-term health side effects; (6) ability to be delivered remotely, without handling animals; (7) minimal effects on individual and social behaviors; and (8) no passage through the food chain (Kirkpatrick and Turner 1991).

The issue of reversibility is not so important in some other species, such as the feral species inhabiting national parks, or species perceived as pests. In North American wild horses, however, public opinion and political pressures require that only reversible contraceptives be applied. The issue of safety in pregnant animals is less important in white-tailed deer, for example, where females are nonpregnant for half the year, as opposed to horses, which have an 11-month gestation that results in pregnancy almost year round. Also, behavioral effects are of lesser importance in species with less complex social organization. Thus, although the stated characteristics are general, each one has greater or lesser importance with any particular species.

At the same time, a fundamental three-step approach to wildlife contraception was envisioned (Kirkpatrick and Turner 1995). Step one consisted of answering the question of whether a particular agent was capable of inhibiting fertility in a particular species. Domestic animals and captive zoo animals provide a wonderful opportunity to answer this question without the expense and complicated logistics of working in the field. Step two was the question of whether the agent could actually be delivered to wild animals under field conditions. The importance of this question is immense. It is one thing to treat a captive deer and quite another to get a dart into a deer that has the ability to elude hunters with real guns. However, if the drug cannot be delivered, it has no practical value. Step three was the question of whether a population effect could be achieved in the field, which is the ultimate goal of any wildlife contraceptive effort. This last question is really just another way of asking if a sufficiently large portion of the population can be treated in any given year. These three steps are absolutely fundamental, but steps two and three usually escape the general public's grasp of the concept of wildlife contraception, and leave the would-be consumer with a concern only whether there is an agent that can actually inhibit fertility in a particular species.

This brief historical review should frame the difficulties of wildlife contraception beyond the pure science of contraceptive compounds. It is within this complex milieu that more recent and sometimes successful wildlife contraception has evolved. In actuality, there are additional constraints to successful wildlife contraception, in the form of political opposition, cultural objections and taboos, and even economic arguments that entwine themselves throughout the issue, but these are not addressed here. A summary of free-ranging species that have been treated with contraceptives is given in Table 13.1.

EQUIDS

In 1971, the issue of wildlife contraception was energized with the passage of the Free-Roaming Wild Horse and Burro Act, which gave almost total protection to horses and burros living on public lands in the United States. This legislation, however, was passed without any evidence of concern for future population control. During the ensuing 10 years, research explored inhibition of stallion fertility by administering a long-acting androgenic compound, testosterone propionate (TP). The theory was that the androgen would feed back to the hypothalamus and/or pituitary and block the release of luteinizing hormone (LH), thereby preventing spermatogenesis. After lengthy and successful trials with domestic pony stallions, Kirkpatrick et al. (1982) and Turner and Kirkpatrick (1982) reported successfully inhibiting reproduction in free-ranging wild stallions by 83 percent in Challis, ID, by lowering sperm counts and motility. Each stallion was given 2.5 to 10 g TP, incorporated in slow-release lactide-glycolide microcapsules (Southern Research Institute) suspended in polyethylene glycol. Although the approach worked pharmacologically, the animals had to be immobilized from a helicopter and then hand injected. The resulting stress and danger of injury rendered this approach impractical.

In a subsequent experiment designed to test the effectiveness of male contraceptives, wild stallions were vasectomized and reproductive success was studied in their respective bands (Asa 1999). Within the bands held by vasectomized stallions, 17 and 33 percent of bands ($n = 40$ in two areas) produced foals, indicating that either bachelor stallions or subordinate stallions were breeding mares successfully. Among the bands headed by intact stallions, 86 and 88 percent of bands had foals.

Table 13.1
Studies of contraceptives in free-ranging wildlife

Family	Species	Method	Reference
Equidae	*Equus caballus*	Testosterone proprionate	Kirkpatrick et al. 1982; Turner and Kirkpatrick 1982; Kirkpatrick 1995
		Vasectomy	Asa 1999
		Estrogen/progesterone	Plotka and Vevea 1990; Eagle et al. 1992
		GnRH vaccine	Goodloe et al. 1996
		PZP vaccine	Kirkpatrick et al. 1990, 1991, 1992, 1995; Turner and Kirkpatrick 2002; Kirkpatrick and Turner 2002; Turner et al. 1997, 2001, 2002; Cameron et al. 2001; Stafford et al. 2001
	Asinus asinus	PZP vaccine	Turner et al. 1996a
Cervidae	*Odocoileus virginianus*	MGA	Levenson 1984; Roughton 1979
		DES	Matschke 1977
		hCG vaccine	DeNicola et al. 1996
		Prostaglandin $F_{2\alpha}$	DeNicola et al. 1997; Becker and Katz 1994
		PZP vaccine	Turner et al. 1992, 1996b; McShea et al. 1997; Naugle et al. 2002
Canidae	*Canis latrans*	DES	Brushman et al. 1967
	Urocyon cinereoargenteus	DES	Oleyar and McGinnes 1974
	Vulpes fulva	DES	Allen 1982
	Lycaon pictus	Deslorelin	Bertschinger et al. 2002
Felidae	*Panthera leo*	MGA	Berry 1996; Orford 1978, 1996; Orford and Perrin 1988
	Felis catus	Megestrol acetate	Remfry 1978; McDonald 1980
	Panthera pardus	Deslorelin	Bertschinger et al. 2001, 2002
	Acinonyx jubatus	Deslorelin	Bertschinger et al. 2002
Elephantidae	*Loxodonta africana*	PZP vaccine	Fayrer-Hosken et al. 1999, 2000; Nave et al. 2000
Petauridae	*Macropus eugenii*	Levonorgestrel	Nave et al. 2000
	Macropus giganteus	Levonorgestrel	Nave et al. 2001, 2002; Poiani et al. 2002
Phocidae	*Halichoerus grypus*	PZP vaccine	Brown et al. 1996, 1997a, 1997b
Aplondontidae	*Cynomys ludovicianus*	DES	Garrott and Franklin 1983
Mustelida	*Mephitis mephitis*	DES	Storm and Sanderson 1969
Procyonidae	*Procyon lotor*	Levonorgestrel	Bickle et al. 1991
		Levonorgestrel	Kramer 1996

GnRH, gonadotropin-releasing hormone; PZP, porcine zona pellucida; MGA, melengestrol acetate; DES, diethylstilbestrol; hCG, human chorionic gonadotropin.

This work more or less ended attempts at stallion-focused fertility control in wild populations.

In a second attempt to inhibit fertility in wild horses, Silastic (Dow Corning) rods containing estradiol (E, 4 g), progesterone (P, 6 g), or ethinylestradiol (EE, 1.5 to 4 g) placed in captive and free-ranging mares reduced reproductive rates by 75 to 100 percent in the captive groups (Plotka and Vevea 1990; Eagle et al. 1992). In this approach, the steroids would interfere with the feedback mechanisms for LH, and possibly for follicle-stimulating hormone (FSH) as well, to prevent follicular development or ovulation. Today, however, we know that neither the TP-based approach with stallions nor the estrogen–progestin-based approach with mares would be permitted because of regulatory issues associated with passage of these compounds through the food chain.

By the 1980s, interest was expanding from steroids to immunocontraception. Goodloe et al. (1996) tested GnRH conjugated to keyhole limpet hemocyanin (KLH) in wild mares at Cumberland Island National Seashore, GA. In theory, the GnRH vaccine would prevent ovulation by blocking the action of LH. The vaccine was freeze-dried and delivered by biodegradable biobullets (BallistiVet) but, although significant antibodies were formed against the vaccine, contraception failed.

A breakthrough occurred in 1988, when, based on the earlier work of Liu et al. (1989) with captive horses, a porcine zona pellucida (PZP) vaccine was delivered remotely to 26 wild mares at Assateague Island National Seashore (ASIS). None of the mares that received an initial inoculation of 65 µg PZP plus Freund's complete adjuvant (FCA) followed by one or two 65-µg booster inoculations plus Freund's incomplete adjuvant (FIA), administered between February and April by means of darts, were pregnant in 1989. Furthermore, 15 of the mares that were pregnant at the time of inoculation delivered healthy foals (Kirkpatrick et al. 1990). The two-inoculation regimen worked as well as the three-shot regimen. Antibodies against PZP caused steric hindrance of the sperm receptor on the mare's own zona pellucida and blocked fertilization (Liu et al. 1989). A year later, half the animals were given a single booster inoculation with FIA, and only 1 of 14 produced a foal (Kirkpatrick et al. 1991). Of related interest was the fact that only two small (25-mm) abscesses occurred at injection sites among all treated animals. In the earlier study, several of the captive animals (Liu et al. 1989) that were inoculated in the neck formed serious abscesses, but in the ASIS studies all inoculations were given in the hip, in the gluteal or semitendinosus muscles.

In a related study, Turner et al. (1996a) demonstrated that the same methodology and dosages worked equally well in free-ranging burros (*Equus asinus asinus*) at Virgin Islands National Park. The significance of this work was to show that the same approach would work in nonseasonally breeding equids.

This initial work, and another 3 years of research on ASIS (Kirkpatrick et al. 1992, 1995), led to the first management-level application of contraception in wild horses or, for that matter, in any wildlife. In 1994 the National Park Service instituted management of the 166-animal herd on ASIS using the PZP vaccine. The outcome of that work was that zero population growth was attained in a single year, and the herd has not grown significantly since 1995 (Turner and Kirkpatrick 2002). Over that same period of time it was shown that body condition scores increased, mare and foal mortality decreased, and entirely new age classes appeared among these animals, extending the expected life span by nearly 10 years. Reversibility of contraceptive effects has been demonstrated in animals treated 1 (100 percent), 2 (100 percent), 3 (70 percent), 4 (100 percent), and 5 (100 percent) consecutive years, but a small group of mares (n = 5) treated for 7 consecutive years have not yet returned to fertility (Kirkpatrick et al. 1992, 1995; Kirkpatrick and Turner 2002) after a 9-year hiatus. This long-term research/management program has even demonstrated that mares whose mothers were treated while they were in utero were fertile when they reached sexual maturity. The total cost of this management is approximately $1,500 annually, in addition to the cost of labor. Normally, it takes two shooters about 2 weeks in March and one shooter for another week in August to treat the 50 to 70 mares annually, with a single booster inoculation.

The management-level application of PZP to ASIS mares also indicated that there was a simple alternative to giving two inoculations in the first year. There was some urgency in getting contraceptive management underway because of the rapid increase in the population; however, contraceptive treatment could not begin before a required environmental assessment was completed in 1995. In March 1994, all 73 mares that had never been previously treated were given a single 65-μg PZP plus FCA inoculation, with the intent of merely causing antigen recognition and establishing all animals as "one-shot" mares thereafter, in preparation for management in 1995. The outcome was a surprising 70 percent efficacy from the single inoculation (Turner and Kirkpatrick 2002), which probably resulted from the timing of the inoculation, just before the breeding season, and the use of a powerful adjuvant, FCA. In 1995, all those mares needed only a single 65-μg PZP plus FIA inoculation to maintain the contraceptive effects. The practical point of this experiment was that, if the managers are willing to give only a single inoculation the first year and forgo immediate contraceptive effects, the animals require only single annual booster inoculations thereafter.

Beyond contraceptive efficacy, both short- and long-term safety is a major consideration for managers of wild horses, which seem to attract a good deal of protective attention from wild horse advocacy groups. The 14 years of study on ASIS has provided valuable data regarding reversibility, safety in pregnant animals or animals in utero when the mother was inoculated, and long-term health of treated animals. Reversibility of contraceptive effects is certain among animals treated for 2 to 5 consecutive years, but the time for reversal is highly variable, ranging from 1 to 7 years. Beyond 5 consecutive years of treatment, there is no evidence for reversibility. During the 12 years of study, there has been no evidence of PZP immunocontraception extending the breeding season, nor has survival differed between foals born to treated or untreated mares (Kirkpatrick and Turner 2003). Finally, females that were carried in utero in treated mares were equally fertile, when attaining adulthood, to those born to untreated mothers (Kirkpatrick and Turner 2002).

The ASIS studies provided many valuable lessons on the importance of remote delivery systems (Kirkpatrick 1995). The initial study utilized a relatively heavy and complicated dart system. The loading of the vaccine into the dart required a special syringe, and then the dart had to be hand-pressurized with still another syringe. Barbs had to be removed before use because animals were not being immobilized. Finally, because the darts utilized needles with very small side-port openings, the viscous vaccine–adjuvant emulsion was injected slowly, and the dart often bounced out before the injection was complete. This difficulty led to the need to "lob" darts into the animals, so they would remain for a few seconds before falling out, which in turn restricted range to perhaps 25 m at best. By 1992, a new dart system was tested and found to be more versatile. The darts were smaller and lighter, could be loaded with a standard syringe, and did not require pressurization, relying instead on a powder charge that was detonated by impact. The smaller darts increased the range up to and beyond 50 m, and virtually all expended darts could be located and tested to determine if the vaccine had been injected.

The success on ASIS has led to application of PZP contraception for the wild horses on the Rachel Carson National Estuarine Reserve on Carrot Island, NC; the Shackleford Banks of Cape Lookout National Seashore, NC; Little Cumberland Island, GA; the Pryor Mountain National Wild Horse Refuge, MT; the Little Bookcliff National Wild Horse Range, CO; and the Return-to-Freedom Wild Horse Sanctuary in Lompoc, CA.

Although the PZP vaccine met the tests of the "ideal" characteristics as already outlined quite well, the necessity to administer two inoculations the first year was a definite hindrance. This limitation could be overcome in two ways. In the first case, tested successfully on ASIS in 1994–1995, a single inoculation was given to all untreated mares ($n = 72$) with no regard to contraceptive effects. A year later, when these same mares were given a single inoculation, contraception was better than 90 percent. Thus, the two-inoculation protocol can be avoided if the contraceptive effects during year 1 are ignored.

An alternative to this approach is to incorporate the PZP into some formulation that permits pulsed or delayed release. In an initial attempt, the PZP was incorporated into nontoxic biodegradable lactide-glycolide microspheres (prepared by D. Flanagan, University of Iowa), which on contact with water (that is, tissue fluids after injection) break down into lactic acid and carbon dioxide, releasing the PZP after some period of time. The actual release time can be altered by changing the ratio of lactide to glycolide. Initial tests with this delivery system took place with Nevada wild horses. One inoculation of a bolus of PZP plus Carbopol 934 (B. F. Goodrich) as an adjuvant plus PZP-containing microspheres, suspended in carboxymethylcellulose, resulted in a degree of fertility control that did not differ from the standard two-inoculation protocol (Turner et al. 1997, 2001). Although contraceptive results were promising, the microspheres settled out of the carrier medium, clogged syringes and needles, and made remote delivery with darts impossible.

The next step was to produce small cylindrical pellets of lactide glycolide that fit into the needle of a dart. One pellet contained 70 to 90 µg PZP and 150 to 175 µg QS-21 (Cambridge Biotech) as the adjuvant (a water-soluble saponin). A second pellet contained a larger dose of PZP, and a third contained 250 to 500 µg PZP. As the PZP–Freund's adjuvant bolus was pushed from the dart, the pellets would embed in the muscle tissue and release at some predetermined time. In January 2000, 96 free-ranging wild mares were treated with these pellets, and, in 2001, 6 percent of the treated mares ($n = 32$) produced foals whereas 59 percent of 33 untreated mares produced foals (Turner et al. 2002). After 2 years, the efficacy was 83 percent (J. W. Turner, personal communication).

A wild horse immunocontraceptive study in New Zealand conducted in the early 1990s illustrates the importance of both adjuvants and delivery systems (Cameron et al. 2001). The Kaimanawa wild horse herd inhabits a military reservation on central New Zealand's North Island. Twenty-six mares in nine different bands were treated with PZP, another 8 mares were given a placebo, and 68 mares were untreated to serve as controls. Seventeen of the treated mares received a second treatment about 2 months after the first. Each mare received 400 µg PZP incorporated into a biobullet, along with 20 µl synthetic trehalose dicorynomycolate (TCDM; RIBI ImmunoChem Research, 25 mg/ml) and squaline oil. The biobullet (BallistiVet) is a solid biodegradable projectile that is nontoxic and erodes on contact with tissue fluids.

Only a single vaccinated mare did not produce a foal a year later, and the causes for the failure were multiple. First, the choice of adjuvant probably resulted in

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poor immune responses. In an earlier controlled study with captive Kaimanawa mares (Stafford et al. 2001), immunization with PZP plus TCDM resulted in highly variable antibody titers in mares regardless of whether they received one, two, or three inoculations. Although the titers rose in treated mares, compared to control mares, they did not increase in steps after each new vaccination, as is commonly seen with better adjuvants, such as Freund's (Lin et al. 1989). Second, the delivery of the biobullets in the field, as opposed to corrals in the controlled study, was difficult because of limited range (20 m) and inability to determine accurately whether the animal was hit at all. Only if a trickle of blood at the target site was witnessed by the shooter was there any indication that the bullet had in fact hit the animal. Finally, the 400-pg PZP dose was considerably lower than the 65-µg dose used in the American studies. Collectively, the poor choice of adjuvant, the limitations posed by the biobullet compared to injecting darts, and the low PZP dose rendered this study unsuccessful, which highlights the importance of each parameter in conducting successful wild horse immunocontraceptive studies.

CERVIDS

The successful application of PZP to wild horses led directly to its use in zoo animals, and soon it was evident that this same vaccine worked in a variety of cervids (Kirkpatrick et al. 1996). In turn, this spawned interest in applying the vaccine to white-tailed deer inhabiting urban and suburban areas of the United States, where traditional lethal methods are no longer legal, wise, safe, or publicly acceptable. After several studies with captive deer (Turner et al. 1992, 1996b) that demonstrated the effectiveness and reversibility of PZP in white-tailed deer, a study was mounted with semifree-ranging deer at the Smithsonian Institute's Conservation and Research Center in Front Royal, VA. This study showed that two 65-µg PZP inoculations are necessary for contraception the initial year, that annual 65-µg PZP boosters will maintain the contraception, and that contraception resulted in an extended breeding season for this species, increasing it by as much as 2 months, a phenomenon that, as already discussed, does not occur in wild horses.

The study also demonstrated the same phenomenon that was seen on ASIS with wild horses; that is, that a single inoculation in the first year would not achieve appreciable levels of contraception, but a single inoculation a year later was successful in inhibiting fertility (McShea et al. 1997). There was no histological evidence of damage to the ovary after 2 years of treatment. These particular deer were extremely wary, so a variety of strategies had to be employed to inoculate all the animals in the study. However, despite the difficulties, it was demonstrated that wild deer could be treated successfully.

Three additional deer projects were mounted soon afterward. The first, which remains unpublished, involves deer within the Metro Parks system of Columbus, OH. Following a cull, PZP contraception has been applied every year since 1995, with favorable results in terms of preventing a rapidly growing population (J. W. Turner, personal communication). The most ambitious deer project was established on Fire Island National Seashore (FINS), NY, in 1993. The island, 55 km long, is a mosaic of established communities interspersed by national seashore, under the authority of the National Park Service. Deer populations within the communities were dense, and the problems were exacerbated by local residents feeding the deer large quantities of high-quality grains.

Because the deer were habituated to humans, several permanent residents of the island could identify deer using the same methods applied to wild horses on ASIS. From 1993 through 1997, 74 to 164 individually identified does were treated with 65 µg PZP plus FCA followed by booster inoculations of 65 µg PZP plus FCA, using blowguns. Between 1993 and 1997, fawning rates among individually identified animals declined by 78.9 percent from pretreatment levels. Population density in the most heavily treated area increased by 11 percent per year from 1995 through March 1998 and then declined by 23 percent per year through 2000 for a net reduction of almost 50 percent (Naugle et al. 2002). This study was the first demonstration that unrestrained deer populations could actually be reduced using contraception.

A third major deer project was initiated in 1993 on the grounds of the National Institute of Standards and Technology (NIST) in Gaithersburg, MD. This high-security facility, belonging to the US Department of Commerce, was inhabited by 185 deer in 1995 to a high of 300 deer in 1997. The deer were either immobilized, hand captured (in the case of fawns), or box-trapped and ear-tagged. Beginning in 1996, an initial 65 µg PZP plus FCA inoculation was given by hand injection, and boosters (same dose with FIA) were given by dart. During the course of the 6 years, a variety of other adjuvants was tested, including Carbapol, ISA-50 (Seppic), and RIBI adjuvant system. Carbapol is a long-chain carbohydrate; ISA-50 consists of 85 percent mineral oil and 15 percent mannide oleate; and the RIBI adjuvant system consists of monophosphoyl lipid A, synthetic trehalose dicorynomycolate, and bacterial cell-wall skeletons. Treated females produced a mean of 0.59 fawns per female in 1997, and then the mean declined to 0.17 to 0.26 fawns per female from 1998 through 2000. As the proportion of does receiving treatment increased to 80 percent in 1998, population fertility declined and the population declined from a high of 300 in 1997 to 218 by May 2001 (Rutberg et al. 2004).

In a slightly different approach, DeNicola et al. (1996) administered human chorionic gonadotropin (hCG: Sigma BioChemical) conjugated to ovalbumin/saponin to two herds of free-ranging white-tailed deer. The formulation, incorporated into biobullets (Antech), was delivered in October and November. All control and hCG-treated deer fawned the following spring. Twenty-one of 58 does were given booster inoculations of porcine luteinizing hormone (pLH: Sioux Biochemical) in the second year, in September and October, and efficacy was determined the subsequent spring. The boosted does actually had a higher fawning rate than the control does, suggesting that pLH enhanced reproduction.

In an attempt to induce abortion in two herds of semifree-ranging white-tailed does, DeNicola et al. (1997) administered 25 mg prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$: Parke-Davis) in biobullets to 18 does in February (which is approximately 94 to 95 days into the approximate 200-day gestation). None of the 18 does produced fawns following treatment. In a repeat of that experiment, only 38 percent of another 8 does captured and treated in the same manner produced fawns, which was a significant reduction compared to control groups. These experiments were important in that they confirmed that $PGF_{2\alpha}$ was an effective abortifacient if given before day 150 of gestation, during which deer rely upon ovarian progesterone to maintain pregnancy. Earlier experiments with hand-injected captive deer using an aqueous solution of $PGF_{2\alpha}$ (Becker and Katz 1994) were unsuccessful. The interpretation of the success in the study by DeNicola et al. (1997) was that a slower release resulted from the biobullet delivery, exposing the corpus luteum to the $PGF_{2\alpha}$ for a longer period of time. The difference between the 100 percent efficacy among the 18 does treated remotely and the 62 percent efficacy among the captured animals was attributed to capture-related stress. Plotka et al. (1983) hypothesized that increased stress generates sufficient adrenal progesterone to sustain pregnancies.

Despite some very successful applications of contraception to wild deer populations, resistance from state fish and game agencies and a requirement by the Food and Drug Administration of treating only ear-tagged animals prevented a wider application of the technology to urban deer.

In 1995, resource managers at Point Reyes National Seashore, CA, began considering the use of contraception in its Tule wapiti herd (*Cervus elaphus nannodes*). These wapiti were the descendants of 10 animals translocated there in 1978, and by 1998 the herd had reached 549. As with most national parks hunting was not an option, and public opinion was not on the side of culling by the National Park Service (NPS). Beginning in 1997, 29 adult cows were initially treated with 100 µg PZP plus FCA by hand injection. Booster inoculations of 100 µg PZP plus

FIA were delivered remotely, by dart, 3 to 6 weeks later. In 1998 another 29 adult cows were treated in the same manner, and 15 of the 1997 cohort were treated with boosters. In 1999 the remaining 50 wapiti cows that had been treated in 1997 and 1998 were given boosters as described. The contraceptive efficacy for the 1997 and 1998 treated cohorts was 97 and 84 percent, respectively. Of the 14 cows that were not given booster inoculations in 1998, 36 percent had calves within 1 year of treatment. Untreated control calving rates during this time were 77 percent (Shideler et al. 2002).

In the only other contraceptive attempt with free-ranging wapiti, Heilmann et al. (1998) examined behavior changes among 10 radio-collared cow wapiti in Idaho. Animals were treated with 65 µg PZP plus FCA for the first inoculation and 65 µg ZP plus FIA for the booster inoculation. As expected on the basis of the McShea et al. (1997) study with deer, the treated wapiti extended their breeding behaviors, described as sexual interactions, well beyond the normal early fall breeding season. Beyond that, there were no changes in social structure or activity patterns.

FELIDS

Contraception has been attempted in a variety of wild felids. The justification for slowing population growth in animals such as the African lion (*Panthera leo*), cheetahs (*Acinonyx jubatus*), and leopards (*Panthera pardus*) is built on (1) the economics of smaller to medium-sized game parks in Africa and (2) changing agricultural practices, which in turn promote large increases in lion populations. As income from agriculture continues to fall, many ranches in South Africa have turned to ecotourism. A portion of the agricultural land is turned over to wild game populations, and an infrastructure is developed to house and transport tourists who are interested in viewing wildlife. A single pride of lions, or perhaps two prides, is tolerable with regard to the numerous ungulate populations inhabiting these small parks, and even desirable so far as tourists are concerned. However, as the lion populations grow, ungulate viewing opportunities decrease, and more animals must be translocated to the park, at great expense, to maintain adequate viewing opportunities.

In Namibia, changing agricultural practices have resulted in unprecedented increases in lion populations. Before the influence of modern man on agricultural practices, ungulate populations migrated large distances in response to drought and rainy seasons. Lions had to follow these migrations, resulting in high cub mortality. With the advent of fencing, artificial water sources, and the disruption of migrations, lion cub survival caused populations to rise to unprecedented and unacceptable levels (Berry 1996).

The first published attempts at applying fertility control to free-ranging lions occurred in Namibia's Etosha National Park in 1981. Based on previous successful experiments with captive lions (Seal et al. 1977), 10 lionesses were implanted with melengestrol acetate (MGA) Silastic implants, marked, and released. Over a 3-year period none of the implanted lionesses produced cubs. On removal of the implants, all returned to normal fertility. None of the implanted lionesses displayed any estrous behaviors while harboring the implants, implying ovulation failure (Orford 1978, 1996; Orford and Perrin 1988). Contraception was discontinued after 3 years because of a decline in lion populations for unrelated reasons. Dosages for the implants were not given in any of the publications, but previous work with zoo lions suggests that the implants contained approximately 500 mg MGA (Seal et al. 1977).

There are no other published reports of the use of MGA implants in free-ranging lions or other large cats, perhaps because of the reports that began emerging at about the same time of pathogenic effects of this steroid on the reproductive system of the recipient animals (Kollias et al. 1984; Linnehan and Edwards 1991; Vollset and Jakobsen 1986).

Orally delivered steroids have been used successfully to inhibit reproduction in feral domestic cats (*Felis catus*). In a field study in Scotland, an initial dose of 5.0 mg megestrol acetate was delivered in meat baits to 15 cats, followed by 2.5 mg per week thereafter. Only 4 of the 15 cats had litters (Remfry 1978). A repeat of this experiment in England was also successful (McDonald 1980).

More recently, interest has turned to GnRH agonists. In an initial experiment with deslorelin, 6-mg long-acting implants were placed in 4 female and 4 male cheetahs and 1 female leopard. Implants of 12 mg were placed in 2 lionesses living under semifree-ranging conditions (Bertschinger et al. 2001). None of the females became pregnant; although the 2 lionesses and the 4 cheetahs showed clinical signs of estrus, they did not permit mating. Within 12 to 18 months clinical signs of full estrus reappeared in 1 of the lionesses, suggesting reversibility of contraceptive action. The male cheetahs showed no evidence of sperm by day 82 after treatment, and 2 nontreated females living with these males did not become pregnant. The study was expanded to 31 cheetahs, 10 lionesses, and 4 leopards, which were either semifree ranging or completely free ranging, in Mabula Nature Reserve, RSA. The results were essentially the same (Bertschinger et al. 2002), and no behavioral side effects were noted. Because the implant matrix containing deslorelin degrades over time without the need for removal (Trigg et al. 2001), this approach may be ideal for free-ranging carnivores that can be captured only once for insertion.

ELEPHANTIDS

During the 1980s, a dramatic decrease in wild African elephant (*Loxodonta africana*) populations occurred, from an estimated 1.3 million in 1979 to about 600,000 in 1989, as a result of poaching for ivory and droughts (Poole 1994). Increased protection by organizations such as the Kenya Wildlife Service and the South African National Parks Board reversed these trends, and African elephant populations have been growing at significant rates since 1990. In Kenya growth rates have been estimated at 4 percent annually (Moss 1994), and in the Kruger National Park in South Africa growth rates have exceeded 5 percent (Joubert 1986). The years of heavy poaching have forced many elephant populations to seek refuge in smaller, compressed habitats, and at the same time much of their former habitat has been converted to agricultural use, which is largely incompatible with elephant populations. Now, despite elephant numbers being smaller than in the 1970s, population control methods, and in particular culling, have had to be implemented throughout many Africa nations.

In 1992, a pilot project was initiated in Kenya to test the effectiveness of the PZP contraceptive vaccine in free-roaming elephants. A small population was inoculated but the project was never completed because of lack of funding by the Kenya Wildlife Service. However, results from analysis of several blood samples indicated that the cows were making antibodies against the vaccine (B. Dunbar, personal communication).

Beginning in 1996, a large-scale project to test the contraceptive efficacy of the PZP vaccine was initiated in the Kruger National Park in South Africa. Ovaries recovered from culled elephants were incubated with rabbit anti-PZP-labeled antibodies, and binding indicated that there was significant cross-reactivity between the antibodies and the elephant zona pellucida (Fayrer-Hosken et al. 1999). In the initial experiment, 21 cow elephants were immobilized, radio-collared, and treated with 600 µg PZP in synthetic trehalose dicorynomycolate (S-TDCM; RIBI Immunochem Research). Inoculations were given on days 0, 30, and 270. The two booster inoculations were given remotely by dart from a helicopter. A year later 18 of 20 control cows were pregnant, whereas 9 of 19 treated cows were pregnant, representing a significant reduction in pregnancy rate. A second group of 10 cows were captured and treated at days 0, 14, and 42, and a year later only 2 were pregnant (Fayrer-Hosken et al. 2000).

To test both the extension of contraceptive effects through booster inoculations and the reversibility of contraceptive action, seven of the cows originally treated in 1996 were recaptured. Four were given 400 μg PZP plus S-TDCM booster inoculations and three were left untreated. A year later none of the four treated cows was pregnant, and ultrasound examinations indicated that all three cows that had not received booster inoculations were pregnant. Ultrasound images of ovaries and uteri of nonpregnant animals appeared normal, and the former showed evidence of healthy follicles and corpora lutea, indicating normal cycling activity (Fayrer-Hosken et al. 2000).

Based on the success of these trials with free-ranging elephants, a new project was initiated at Makalali Private Game Reserve, South Africa. In this project, all PZP vaccine was delivered remotely by dart, from the ground, and social behaviors and time budgets were studied (Delsink et al. 2002). Eighteen cows were treated with either 400 or 600 μg PZP plus Freund's modified adjuvant. Minor changes in family group movements and time budget utilization occurred immediately following treatment, but these returned to pretreatment values within 2 weeks after treatment. Four of the treated cows were pregnant at the time of treatment, and all produced healthy calves, indicating that PZP treatment did not interfere with the health of the calves in preexisting pregnancies. Preliminary results gathered in 2003 suggest that contraception is effective (A. Delsink, personal communication).

MACROPODS

Two different marsupials have presented Australians with overpopulation dilemmas. The eastern gray kangaroo (*Macropus giganteus*) is the counterpart to the urban white-tailed deer in North America in that it inhabits densely human-populated areas and industrial sites and represents a real or perceived nuisance, safety hazard, agricultural damage, and sometimes a threat to biodiversity. The koala (*Phascolarctos cinereus*) is found only in small numbers in some of its historic range, but on island and fragmented forest habitats it often exceeds habitat carrying capacity, thus requiring some form of population control. Additionally, brush-tailed possums (*Trichosurus vulpecula*) translocated to New Zealand represent a marsupial pest in that country.

Because the neuroendocrine control of folliculogenesis and ovulation is similar in marsupials and eutherians, the possibility of utilizing synthetic progestins to inhibit marsupial fertility was investigated. The tammar wallaby (*Macropus eugenii*) was selected as a model, and the synthetic progestin levonorgestrel (LNG) was administered in the form of Norplant implants (Leiras Pharmaceutical) (Nave et al. 2000). Each implant contained 70 mg LNG and was assumed to release the drug at the same rate as in women, 30 µg/day initially and then 15 mg/day after 12 months (Sivin 1988). Among control animals, 86 percent gave birth to new pouch young, 88 percent mated at the end of the first estrous cycle, and thereafter 94 percent produced young. Normal reproductive activity, defined as reproductive behaviors, breeding, and production of offspring, continued through 48 months. Among 24 implanted wallabies, only 42 percent gave birth at the end of the first cycle and none bred or produced young after that.

The same type of implant was next tested in a wild free-ranging population of eastern gray kangaroos. Seventeen kangaroos were captured and anesthetized, and each female received two implants subdermally. Eight control females were given empty rods, and all animals were released. A year later 7 of the control females (88 percent) produced young, and 3 of the treated females (19 percent) produced young (all 3 had pouch young at the time they were implanted, indicating that they were already in a diapause pregnancy). At the end of the second year all 8 control females and none of the treated females produced young (Nave et al. 2001, 2002; Poiani et al. 2002). There was no difference between the control and treated groups with regard to time spent feeding and grooming, although more males associated with control females.

PINNIPEDS

Porcine zona pellucida incorporated into multilaminar liposomes was administered to grey seals (*Halichoerus grypus*) on Sable Island, Nova Scotia. Sixty-four 14-year-old females, seventeen 20-year-old females, and twenty 21-year-old females were inoculated a single time with 100 µg PZP in 0.5-ml liposomes emulsified with 0.5 ml FCA. Over a 5-year period the birth rate, based on the return or failure to return to breeding grounds, dropped significantly among treated animals. Treated animals that did return were caught and bled, and antibody titers against the PZP were measured. The determined threshold for a contraceptive titer was 5 percent of reference serum standards, which is remarkably low compared to titers in other species (Brown et al. 1996, 1997a, 1997b).

RODENTS

The history of rodent contraception is another example of large numbers of studies occurring with captive wild or laboratory rodents under carefully controlled conditions with few actual published reports of application, or even study, with free-ranging populations. Some of the earliest attempts at wildlife contraception occurred with captive rodents, such as mice (*Mus* sp. and *Peromyscus* sp.) and voles (*Microtus* sp.), using a variety of steroid compounds (reviewed by Kirkpatrick and Turner 1984), but problems associated with bait acceptance, similar to those seen with deer, coyotes, and foxes, prevented field application. Several more recent studies have been conducted to assess the role of fertility control in rodents, but the methods used involved only castration or tubal ligations, which by definition are not contraception.

The only true contraceptive study with wild rodents occurred with the black-tailed prairie dog (*Cynomys ludovicianus*). Garrott and Franklin (1983) fed prairie dogs inhabiting Wind Cave National Park diethylstilbestrol (DES) incorporated into an oat bait. The DES was mixed with hulled oats at a concentration of 0.11 percent, and 25 g was placed at each active burrow twice per week, in March, just preceding the breeding season. After 1 year, 5 of 13 treated females (38 percent) produced litters, and after 2 years, 17 of 21 treated females (81 percent) produced litters. By year 3, 8 of 13 (62 percent) control females produced litters whereas no litters were produced by 21 treated females. In year 4, control reproductive success rose to 89 percent, and treated animals produced no litters at all. No later reports of this approach have appeared, probably because of the environmental issues surrounding the incorporation of a powerful antifertility steroid in prey species utilized by a variety of raptors and predatory mammals.

MUSTELIDS

Only two published reports exist for studies of contraception in wild mustelids. In the first study, DES-loaded egg baits were put out in striped skunk (*Mephitis mephitis*) habitat, but poor bait acceptance and erratic bait consumption led to unsuccessful results (Storm and Sanderson 1969). In a second study with free-ranging striped skunks, Norplant implants were placed in radio-collared females. One implant was placed in each skunk, and a year later none of the four recovered treated animals was pregnant or lactating (Bickle et al. 1991). Although this latter study was short term, it corroborates the effectiveness of Norplant implants in kangaroos (Nave et al. 2002) and the active ingredient levonorgestrol (LNG) in domestic cats (Looper at al. 2001).

This approach appears attractive for small mammals inhabiting urban areas, such as raccoons and skunks, where capture is relatively easy and where the chance for passage of the LNG to predator species is minimized. However, the possibility of deleterious effects of synthetic progestins in carnivores was not resolved by this study, and long-term investigations are needed. It has been estimated that skunks inhabiting urban areas do not normally live for more than 2 to 3 years; thus, any deleterious effects of progestins in this species in this setting may not be serious. The cost of the implants, however, probably precludes their widespread use in the near future.

PROCYONIDS

Only a single study exists for attempts at contraception in wild raccoons, that of Kramer (1996) using levonorgestrel (LNG) implants in free-ranging raccoons (*Procyon lotor*) on Canaveral National Seashore, FL. The implants were the same as those used in the skunk studies of Bickle et al. (1991) and the kangaroo studies of Nave et al. (2002), and each contained approximately 70 mg LNG with a release rate of 30 µg/day. The attempt failed because the application of this progestin, and probably others as well, can block parturition in the pregnant female, potentially causing LNG to be lethal if given to pregnant animals (see discussion in Chapter 7, Contraception in Carnivores). A previously unpublished study, conducted with LNG implants in captive raccoons, in tandem with the skunk study of Bickle et al. (1991), showed that LNG will inhibit fertility in nonpregnant raccoons (at a rate of two implants per animal). That study was conducted in Iowa, where raccoons are exclusively seasonal with regard to reproduction and where all treated animals were nonpregnant, whereas the raccoons on Canaveral National Seashore were not seasonal and some were pregnant at all times of the year. Thus, this approach might only be useful in more northern climates, where animals could be treated during the late summer and fall, when they were not pregnant. The LNG implants did not alter home range size, compared to controls. Although this experiment was not successful, the possibility of using LNG implants in urban raccoons in northern latitudes has some potential.

SUMMARY

The recent application of contraceptives to free-ranging wildlife management suggests fertility control is a reasonable approach to population management in some species. There is an impressive array of research in progress aimed at wildlife contraception, but most of this work is still at a stage where its use is confined to captive populations. As this research moves forward, the investigators must pay more attention to the problems and logistics of actual application in the wild or a great deal of effort and money will be lost. It is obvious that we need more and better contraceptive compounds and vaccines, but the greatest needs are for delivery systems and qualified and trained personnel to carry out the work in the field.

Delivery can be oral, by implant or hand injection after capture, or by dart in unrestrained populations, but the contraceptive agent must be compatible with the delivery system, and those problems must be addressed during development of the compounds and agents. Successful delivery of contraceptives to wild populations requires extraordinary understanding of the target species natural history and behavior as well as effective and safe dart delivery technology. Finally, not just anyone can move from the laboratory to the field and be successful. The qualities inherent in successful field operatives are often less tangible than those for a fine molecular biologist or immunologist.

The development of newer and better contraceptives must also be carried out in concert with regulatory agencies, such as the Food and Drug Administration or the US Department of Agriculture (USDA), or the results may be effective contraceptive technology that will not be permitted in the field (for discussion, see Chapter 2, Regulatory Issues). For example, it is unlikely that any orally delivered wildlife contraceptive will be licensed by a regulatory agency unless it is species specific, at least in the United States, yet research groups often pursue this approach without even a preliminary meeting with the regulators.

The economics of wildlife contraception pose special problems and hurdles to advancement. Most major pharmaceutical companies, or even small proprietary drug companies, must think in terms of sales of millions of doses per year to make acceptable profits. At the same time, the numbers inherent in wildlife contraception, far fewer than millions of doses per year, preclude the specific development of wildlife contraceptives for commercial reasons. No company will recover its investment if the only use for the contraceptive is in wildlife; thus, research advances will be slow unless there is an application for companion animals or domestic livestock as well. The cost of bringing a new drug or vaccine to commercial development is well beyond the expected returns from a successful product. Thus, wildlife contraceptive development will continue to creep along with nonprofit groups, or perhaps a bit faster in government-funded agencies such as the USDA or Commonwealth Scientific and Industrial Research Organisation (CSIRO) in Australia.

Finally, the entire subdiscipline of wildlife contraception is laced with political, social, cultural, and economic issues that can stop even the best technology dead in its tracks. There are ethical and moral issues surrounding this field, and those who nobly pursue more humane approaches to wildlife management may run afoul of one or more opposition groups, including animal rights groups, hunters, or those who cannot accept change. Ultimately, the scientists who pursue this goal, regardless of their altruism or lack thereof, must listen carefully to the true owners of all this wildlife—the public—if they are to be successful.

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