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Fertility Control in Animals

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CHAPTER

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From Mortality Control to Fertility Control

For most of the twentieth century, government agencies charged by law with managing wildlife were dedicated to building the size and productivity of populations of game species. Under a utilitarian philosophy of wildlife conservation, this dedication made sense and, in its time, was arguably a highly progressive view of wildlife (Dunlap 1988).

In the United States, state game management went far to reverse the wildlife catastrophe of the nineteenth century. In the 1800s hunting and trapping for commercial markets drove Carolina parakeets and passenger pigeons extinct and nearly extirpated bison, elk, deer, beavers, egrets, waterfowl, songbirds, and any other furred or feathered creature that could make a meal or adorn a hat (Tober 1981). Predatory birds and mammals were shot on sight because of the threat they posed to domestic livestock and poultry and because they were believed by some to be genuinely evil (Dunlap 1988).[1]

Through an aggressive program of reintroduction, habitat management, and restrictions on killing, state wildlife agencies succeeded in restoring populations of deer, elk, beavers, otters, waterfowl, and other game and fur-bearing species (Gilbert and Dodds 1992). The linchpin of this effort was recreational hunting and trapping, which furnished funding (through license sales and Pittman-Robertson grants), volunteer labor, and a dedicated political constituency.

At the beginning of the twenty-first century, this neat system is unraveling. Demographic changes are producing a shrinking and aging population of hunters and trappers (hunters, for example, now represent only 7 percent of the total U.S. population) (U.S. Fish and Wildlife Service 1997); a growing public appreciation of "nongame" species that have been neglected, and even harmed, by management of game species; and changes in public values, from utilitarian views to moral views of wildlife (Kellert 1985; Dunlap 1988). The biggest challenge to the system may arise from the failure of state agencies to respond effectively to the problems associated with dense populations of deer, geese, and other species, especially in urban and suburban communities.

How could a system founded on hunting and trapping—killing—find itself unable to control wildlife populations and solve problems associated with abundant wildlife? There are several reasons. Reflecting cultural attitudes—and regulations—that discourage the killing of females, public hunting has focused on removing male deer and other big-game animals, leaving populations streamlined for reproduction. Many of the most severe wildlife conflicts arise in locations that are effectively unhuntable, such as parks, research campuses, and suburban neighborhoods. Killing of some species, such as wild horses, is simply unacceptable to the public. The public's tolerance of invasions of their parks and backyards by armed strangers is declining just as its sympathy for wild animals and its interest in nonlethal solutions to wildlife problems are rising.

While the public is searching for new, humane approaches to solving conflicts with wildlife, state wildlife agencies persist in recommending hunting and its variations. Wildlife agencies in some states, such as New York, are required by law to promote recreational hunting (Marion 1987). But, more pervasively, most state agency personnel have strong cultural and political links to the hunting and trapping community. This community is (somewhat irrationally) hostile to the concept of nonlethal management of wildlife (Kirkpatrick and Turner 1995; Hagood 1997). Wildlife agencies' advocacy of hunting and trapping is coupled with a reluctance to pursue or encourage research into other approaches. As a result, the public is turning elsewhere for solutions.

There are, effectively, only two choices for actively managing the size of animal populations: reducing the birth rate and increasing the death

rate. (Local population size may also be controlled by movement of individuals in and out; but when the size of animal populations concerns us, movement of individuals merely relocates the concerns. We are not absolved of our responsibility for animals simply because they go somewhere else.) Killing certainly can reduce and even destroy wildlife populations if enough animals of the right description are removed from the population. Until the last decade of the twentieth century, however, fertility control for wildlife was not seen as a feasible option.

Everything changed between 1988 and 1989. The successful use of a remotely deliverable immunocontraceptive on free-ranging wild horses at Assateague Island National Seashore, in Maryland, opened a new universe of possibilities for the humane, nonlethal control of wildlife populations.

The History of Wildlife Fertility Control

The history of wildlife fertility control and its application to the management of free-roaming and captive wildlife populations is relatively short, perhaps no more than fifty years. Until the late 1980s, wildlife contraception was a "boutique" subject among scientists and wildlife managers. This lack of interest is a bit surprising, because the technology developed for contraception in humans has been impressive and its application to wildlife is fundamentally sound, at least in a pharmacological context. Various compounds developed for use in humans were first tested in animal models. The resistance to new approaches in wildlife management, which played a significant role in the slow pace of development and interest in wildlife contraception, stem not from science but from a variety of social, cultural, and economic factors.

That said, the history of wildlife contraception can be traced broadly by examining the technological approaches and, more specifically, the nature of the chemicals, hormones, and other compounds that have been applied to various species. Chronologically, these approaches can be classified as (1) nonhormonal chemicals, (2) steroid hormones, (3) nonsteroidal hormones, (4) barrier methods, and (5) immunocontraceptives.

This oversimplification is compounded by the various permutations of chemical agent, delivery system, and specific species. For example, a contraceptive can be delivered (1) orally, (2) by surgically placed implant, (3) by hand-injection, or (4) by remotely delivered dart.[2] The historical development of wildlife contraceptives had to take into account whether the animal was (1) small and easily live-trapped, (2) usually wary and unapproachable, (3) living in a captive setting, (4) capable of being induced to take baits, or (5) classified as a food animal by the U.S. Food and Drug Administration (FDA).

Nonhormonal Compounds

Nonhormonal compounds have been used most extensively in birds. Some of the compounds used were classified as fungicides and seed disinfectants (Arasan®, DuPont Co.) (Elder 1964), others as anticholesterol agents (22,25-diacholesterol dihydrochloride, later marketed as Ornitrol®, G. D. Searle and Co.) (Wofford and Elder 1967). In both cases, fertility was inhibited but toxic effects made the compounds unacceptable. Most of the other compounds used for birds (thiotepta and triethylene melamine) had similar shortcomings (Davis 1959, 1962). In general, nonhormonal compounds were abandoned because of their accompanying toxic effects. While some degree of contraception, and in a few cases sterilization, could be achieved, the administered dose had to be very precise. This was not possible with oral delivery in wildlife. In addition, the mechanisms of action were poorly understood, and it is unlikely that any of these compounds could have passed the rigorous regulatory requirements of today's FDA or Environmental Protection Agency (EPA).

Some nonhormonal compounds were derived from plant products and based on historical evidence that Native Americans used certain plants for contraceptive purposes. A comprehensive review (Farnsworth and Waller 1982) listed fifty plant families with documented antifertility effects in males and females. Despite some controlled tests with laboratory animals (Cranston 1945; Barfneet and Peng 1968) and a few wild species of rodents (Berger et al. 1977) and reports of occasional interference with fertility in humans (Shao 1987), few investigators have attempted to exploit these naturally occurring substances to control reproduction in wildlife. This area remains a fertile subject for interested scientists.

Steroid Hormones

Research into the use of steroid hormones for wildlife fertility control became common in the 1960s and '70s and was based on the research originally directed at human fertility control (Pincus et al. 1958). In general, steroid hormones work as contraceptives by feeding back upon the hypothalamus and/or pituitary glands and depressing gonadotropic hormones, thereby reducing or eliminating ovulation or spermatogenesis, or by changing the speed with which the ovum moves through the oviducts. Diethylstilbestrol (DES, a synthetic estrogen) was introduced into bait and fed to foxes (*Vulpes vulpes)* (Linhart and Enders 1964; Cheatum 1967; Oleyar and McGinnes 1974; Allen 1982), coyotes *(Canis latrans)* (Balser 1964; Brushman et al. 1967), whitetailed deer *(Odocoileus virginianus)* (Harder 1971; Harder and Peterle 1974), and black-tailed prairie dogs *(Cynomys ludovicianus)* (Garrott and Franklin 1983) with significant contraceptive effects. Another steroid, mestranol, which is closely related to DES, was fed to red foxes (Storm and Sanderson 1969), small rodents (voles, rats, and mice) (Marsh

and Howard 1969; Howard and Marsh 1969; Storm and Sanderson 1970), and cats (Burke 1977) with some contraceptive success, but bait acceptance decreased quickly. At about the same time, oral medroxyprogesterone acetate (MPA) was tested in red foxes (Storm and Sanderson 1969). Shortly thereafter, other investigators explored the use of oral progestins for controlling fertility in domestic canids. Oral melengestrol acetate (MGA) was highly effective in inhibiting fertility in dogs (Sokolowski and Van Ravenswaay 1976) and a related compound, megestrol acetate (MA), was approved for commercial use in dogs (Ovaban®, Schering Corporation) (Wildt and Seager 1977).

The use of these and similar oral steroid hormones in wildlife was restricted by problems with bait acceptance and dosage and by environmental concerns, especially effects on nontarget species (all these steroids pass through the food chain). These problems changed the focus of wildlife contraceptive research to more narrowly targeted delivery systems. Steroid hormones were administered via injection or surgicallyplaced implants in wapiti *(Cervus elaphus)* (Greer et al. 1968), large exotic species of cats (Seal et al. 1976), deer (Bell and Peterle 1975; Levenson 1984), and wild horses *(Equus caballus)* (Kirkpatrick et al. 1982; Plotka and Vevea 1990). Significant contraceptive effects were achieved in these species, but several new problems arose. Application of these steroids to free-roaming wildlife required relatively large doses of the compounds, negating the use of remote delivery via darts. This meant that each animal had to be captured before it could be hand-injected or given a surgical implant. This was impractical with most species, because of the stresses associated with capture, the frequency with which the steroid had to be administered, and the large doses that had to be administered. Unknown at the time but evident in later years were various pathologies that resulted from long-term use of these steroids, particularly among (but not restricted to) felids (Buergelt and Kollias 1987). These molecules were also shown to have profound effects upon the behavior of treated animals, something that would be undesirable in valued wildlife species.

Norplant® implants containing levonorgestrol were effective in striped skunks *(Mephitis mephitis)* (Bickle et al. 1991), and raccoons *(Procyon lotor)* (Kirkpatrick, unpublished data), which could be easily captured in live traps in urban settings, but these two species were clearly an exception to the practical application of injectable or implant steroids to larger species.

Nonsteroidal Hormones

Wildlife contraceptive research with nonsteroidal hormones has been largely confined to agonists and antagonists of gonadotropin releasing hormone (GnRH) (Becker and Katz 1997). Normally GnRH signals the pituitary to secrete the gonadotropin luteinizing hormone (LH) or follicle stimulating hormone (FSH), both necessary for normal function in the ovaries and testes. The agonists and antagonists of GnRH block the effects of GnRH on the pituitary by one of several mechanisms. These compounds have been used successfully to inhibit fertility in dogs (Vickery et al. 1984, 1985; Inaba et al. 1996), monkeys (*Macaca* spp.) (Fraser et al. 1987), and a variety of other species. To date, however, these compounds have been short-lived in their effects and require large doses for extended effectiveness.

Barrier Methods

Mechanical birth control devices have been tested in white-tailed deer (unsuccessfully), horses (successfully), and a variety of zoo animals (mixed results), but the logistics of application to free-roaming wildlife are prohibitory in most species. These methods have included IUD-like barriers for the deer (Matschke 1980) and horses (Daels and Hughes 1995) and silastic vas deferens plugs in the zoo animals (Porton et al. 1990). More comprehensive reviews of the history of wildlife contraception exist (Kirkpatrick and Turner, 1985, 1991).

Immunocontraception

More recently, immunocontraception, or vaccine-based fertility control, became a reality for use in wildlife. Immunocontraception is based on the same principles as is disease prevention through vaccination. Humans and other animals are vaccinated against diseases by injections of dead or attenuated disease bacteria or viruses or of molecules that are harmless but similar to toxins the disease organisms produce. The stimulated immune systems then produce antibodies against some essential event or structure in the reproductive process.

A variety of immunocontraceptive vaccines are under development, including vaccines against brain reproductive hormones such as GnRH (Hassan et al. 1985; Ladd et al. 1988, 1989; Bell et al. 1997) and LH (Al-Kafawi et al. 1974) and vaccines against sperm (Primikoff et al. 1988; Herr et al. 1989) and egg (Florman and Wassarman 1985), which prevent fertilization. One of the first immunological approaches was a vaccine against the zona pellucida of the mammalian egg, which was patented as an antifertility agent in 1976 by R. B. L. Gwatkin for Merck and Company (Skinner et al. 1996). In 1988 this vaccine was applied to wild horses with great success. Success with the porcine zona pellucida vaccine (PZP) has opened the door to a practical approach to wildlife fertility control; since then other experiments with antisperm vaccines have been initiated.

The biology of the PZP vaccine, which is derived from pig eggs, is both simple and complex. An extracellular matrix known as the zona pellucida (ZP) surrounds all mammalian eggs. The ZP consists of three major glycoprotein families, one of which, ZP3, is thought to be the principal sperm receptor in most species (Prasad et al. 2000). When the vaccine is injected into the muscle of the target female animal, it stimulates her immune system to produce antibodies

against the vaccine. These antibodies attach themselves to the sperm receptors on the ZP of the target's eggs and distort their shape, thereby blocking fertilization (Florman and Wassarman 1985).

The Art and Science of Wildlife Immunocontraception

In the late 1980s, the failure to achieve practical results and the dangers associated with steroid hormones had led to a reexamination of the problems associated with wildlife contraception. Research had been proceeding without an idealized standard by which to evaluate each new approach. Kirkpatrick and Turner (1991) created such a standard, which included the following goals:

1. Contraceptive effectiveness of at least 90 percent
2. The capacity for remote delivery with no (or minimal) handling of animals
3. Reversibility of contraceptive effects (more important for some species than for others)
4. Safety for use in pregnant animals
5. Absence of significant health side effects, short or long term
6. No passage of the contraceptive agent through the food chain
7. Minimal effects upon individual and social behaviors
8. Low cost

While some of these goals are more or less arbitrary, they at least provided reasonable guidelines for discussion and planning. They were built exclusively around wild-horse contraception and did not address all problems associated with diverse species and settings.

In the development of the PZP vaccine for certain species, some of these problems became clear. The challenge of deer contraception, for example, even in urban areas, was and is to develop a single-dose form of the vaccine that would provide at least one, and perhaps several, years of contraception from one application. (The use of the raw, native form of the PZP vaccine requires two inoculations the first year, which can be very difficult with wary species like deer.) The challenge of elephant contraception, where doses of vaccine must be ten times larger than standard wild-horse or deer doses, raised the need for the development of a synthetic form of the vaccine. The process of producing the native PZP vaccine is laborious, and the number of doses that can be produced in a year is limited at this time by the production process. A synthetic form of the vaccine would expand the application of wildlife contraception beyond present logistical restrictions and eliminate some of the regulatory concerns raised by the use of natural products.

The mere availability of a good physiological immunocontraceptive does not insure its effective application to wildlife. The first step in the development of a wildlife contraceptive is to test its efficacy in captive animals or domestic counterparts, but once this has been done and physiological efficacy has been determined, strategies for application to free-roaming species must be developed. It is a large leap from inoculating a deer in a pen to inoculating a wild free-roaming deer; it's yet another leap from administering the vaccine in the field to controlling a wildlife population.

Actual application to free-roaming species requires a variety of delivery and access strategies. Immunocontraceptives can currently be delivered by intramuscular injection: an animal must be given the vaccine either by hand injection or by a dart. Two delivery systems require at least two access strategies. Hand injection requires physical capture of the target animal; it increases the stress for the target animal, danger to the person(s) doing the work, and expense. Although in some settings, such as zoos, access is not so great a problem, it is not always possible to hand-inject animals without causing some degree of capture-related stress. In other situations, such as with wild horses in the West, hundreds of animals at a time are rounded up for entry into adoption programs, and it is relatively easy to hand-inject animals as they pass through a chute.

For most species of wildlife, the only delivery option is by dart. It has advantages and disadvantages. The most obvious advantage is that it eliminates the need for stressful capture of animals. The small volume of vaccine necessary to immunize an animal (1.0 cc) permits the use of very small and light darts. This increases the effective range of darting and decreases the chances of injury to the target animal. The disadvantages include the need to approach the animal to within fifty meters, the need to separate the animals that have been inoculated from those that haven't, and the labor-intensive nature of the endeavor.

Despite the fact that inoculation of free-roaming wildlife with a contraceptive vaccine is at best difficult, a significant degree of success has been achieved under field conditions.

Wild Horses

Liu et al. (1989) first discovered that the PZP vaccine would inhibit fertility in domestic mares. Soon after, wild horses were treated with the PZP vaccine on Assateague Island National Seashore, in Maryland; studies have continued for twelve years. The vaccine was delivered remotely, with small darts. Contraceptive efficacy was greater than 95 percent (Kirkpatrick et al. 1990). The vaccine was safe to administer to pregnant animals and did not interfere either with pregnancies in progress or the health of the foals born to inoculated mothers. A single annual booster inoculation was sufficient to maintain the contraceptive effects (Kirkpatrick et al. 1991), and contraception was reversible after three and four years of treatment (Kirkpatrick et al. 1992, 1995a, 1996a). No changes occurred in the social organization or behaviors of the treated animals. In 1994 the National Park Service began the

management of the Assateague wild horses via the PZP vaccine and, after only three years, the herd reached zero population growth (Kirkpatrick 1995; Kirkpatrick et al. 1997). This approach as of 2000 was being applied to large wild-horse herds in Nevada (Turner et al. 1996a), and trials with feral donkeys (*E. asinus)* in Virgin Islands National Park have been successful (Turner et al. 1996b).

White-Tailed and Black-Tailed Deer

Populations of white-tailed deer and, to a lesser extent, black-tailed deer *(O. hemionus)* exploded in North America during the last two to three decades of the twentieth century. The causes of the population explosion are undoubtedly complex. It is generally attributed to the use of high-yield crops; the spread of deer-friendly suburbs, which offer a diverse menu of heavily fertilized ornamental shrubs and grasses intermingled with disturbed "natural areas" such as small parks and woodlots; increasingly mild winters; the absence of natural predators; and recreational hunting practices ill-suited to controlling deer populations in suburbs.

With burgeoning deer populations and suburban sprawl has come a rapid rise in conflicts between deer and people. These have centered on an increase in deer-vehicle collisions, damage to crops and ornamental plants, undesirable impacts on some forest ecosystems, and tick-borne zoonotic diseases, particularly Lyme disease (Conover 1997; Rutberg 1997). There is now enormous interest in finding new tools that will allow people and deer to coexist, and much public attention has focused on immunocontraception. In autumn 1997 alone, for example, The Humane Society of the United States (HSUS) received requests for information on deer immunocontraception from people in more than sixty communities across the United States.

The 1988–89 field demonstration on wild horses at Assateague spurred preliminary testing of PZP on captive deer. Effects on captive deer resembled those in wild horses; the two-shot vaccine protocol was highly effective, the vaccine could be delivered remotely, its effects were reversible after at least two years of treatment, and no health side effects were apparent (Turner et al. 1992, 1996c, 1997; Kirkpatrick et al. 1997; see also Miller et al. 1999). A subsequent trial with semi–free-roaming deer at the Smithsonian Institution's Conservation and Research Center, in Front Royal, Virginia, provided evidence that the vaccine could be delivered remotely under field conditions; although there was evidence that PZP treatments extended the mating season, treated females gained more weight than untreated females, presumably because they were spared the energetic costs of pregnancy and lactation (McShea et al. 1997). A study begun in 1993 at Fire Island National Seashore, New York, launched a series of field studies that explored the effectiveness and costs of different field techniques, vaccination schedules, and vaccine preparations, as well as investigated effects of PZP on behavior and survival (Kirkpatrick et al. 1997; Thiele 1999; Walter 2000; Rudolf et al. 2000). The Fire Island study was the first to show that biologically significant numbers of females could be efficiently and effectively treated in the field; approximately 200 females a year were under treatment by 1996. However, vaccine effectiveness in this study was lower than in previous deer studies, especially in the first year following treatment, probably due to incomplete or misdelivered initial vaccinations (Kirkpatrick et al. 1997; Thiele 1999, HSUS unpublished data).

The first demonstration that immunocontraception reduced an unconfined deer population was accomplished at the National Institute of Standards and Technology (NIST). NIST, a 574-acre federal research facility within the city of Gaithersburg, Maryland, supported a deer population of approximately 180 animals in 1993. By the time PZP treatments began in autumn 1996, the population had risen to approximately 250, and it peaked at approximately 300 in autumn 1997 (Thiele 1999). By autumn 1998, however, more than 90 percent of the NIST females were receiving PZP treatments, and the population had declined about 20 percent below peak levels by spring 2000 (HSUS, unpublished data). Good access to deer for treatment, high population mortality (the majority due to vehicle collisions), and relatively low reproductive rate all contributed to success in controlling this population.

Zoo Animals

A third application of the concept of wildlife immunocontraception is the control of the production of "surplus" animals in zoos. Despite often-heard discussions of the challenges of breeding endangered species in captivity, most zoo species breed quite successfully, and the production—and disposition—of surplus animals is perhaps the largest single problem facing zoos worldwide. Beginning in 1990 the PZP vaccine was applied to various exotic species in zoos, beginning with Przewalski's horses *(E. przewalskii)* and banteng *(Bos javanicus)* at the Cologne Zoo (Kirkpatrick et al. 1995b), and five species of deer at the Bronx Zoo (now the Wildlife Conservation Center) (Kirkpatrick et al. 1996b). The PZP vaccine has been tested in more than ninety species in more than seventy zoos worldwide (Frisbie and Kirkpatrick 1998). Today it is reducing zoo births and providing some relief to the problem of surplus animals.

African Elephants

A fourth major application is under way in Africa. Devastated by the lucrative trade in elephant ivory, populations of African elephants *(Loxodonta africana)* were reduced to dangerously low numbers during the 1970s and 1980s. Elephants basically retreated to the sanctuary of national parks. In the meantime, much former elephant habitat outside of these parks has come under intensive agricultural use. In a sense Africa's elephant popu-

lations are now trapped in the national parks. As poaching has diminished, their numbers are increasing by as much as 5 percent per year. Ironically in some areas elephants are now threatening both the ecosystems of national parks and their own health. In recent years this problem has been managed through "culling," a euphemism for shooting. Four African nations currently kill elephants in order to keep populations within the carrying capacity of their parks. (Kruger National Park, in South Africa, killed 300 to 700 elephants annually for thirty years but suspended culling in 1995.) This is tragic, particularly for a species that is believed to understand the concept of death.

In 1995 preliminary experiments provided evidence that the PZP vaccine would work in elephants. Several zoo elephants were treated with the vaccine and, while these were not breeding animals, we determined that they produced antibodies against the vaccine. In October 1996 twenty-one elephants in Kruger National Park were captured, radio-collared, and treated with the PZP vaccine in order to determine its contraceptive efficacy. In November 1996 and again in June 1997, each treated elephant was given a single booster inoculation by means of a dart fired by a shooter in a helicopter. None of the animals was captured for these booster inoculations, proving that elephants need not be captured to be vaccinated (Fayrer-Hosken et al. 1997). In this trial pregnancy rates in elephants were reduced from 90 percent in untreated control animals to approximately 37.5 percent in treated animals. Based on the successful preliminary results, there may be a nonlethal solution to the wise management of park elephants. Additional studies designed to increase the efficacy of the vaccine in elephants were carried out in 1998. In this latest round of trials, fertility was reduced by 75 percent. There were no changes in behavior among the treated animals, the contraceptive effects were reversible, and the reproductive system of the treated animals (uteri and ovaries) remained normal.

Other Species

In May 1997 ZooMontana, under contract to the U.S. Navy, began treating thirty water buffalo *(Bubalis bubalis)* on the island of Guam with the PZP vaccine. Preliminary results indicate that the experiment significantly reduced pregnancies in these animals. These results have led to a new, five-year project by the U.S. Navy and the U.S. Fish and Wildlife Service using PZP to control water buffalo on the U.S. naval base at Guam. This project will set the important precedent of nonlethal control of wildlife by the Department of Defense.

On Point Reyes National Seashore in California, Tule elk *(C. elaphus nannodes)* are being treated with PZP as part of a series of tests to determine whether the herd can be managed with contraception. Preliminary evidence shows that elk can be successfully contracepted with PZP (Kirkpatrick et al. 1996b; Heilmann et al. 1998; Shideler, personal communication).

Research in Progress

The PZP vaccine appears to come close to the optimum contraceptive agent when measured against the "ideal" wildlife contraceptive. So far, at least, its physiological actions appear to be sound and safe; it does not appear to pass through the food chain; and it is not associated with immune responses to somatic tissues (Turner et al. 1997; Barber and Fayrer-Hosken 2000). However, the ideal wildlife contraceptive vaccine would require only a single inoculation in order to achieve several years of contraception. It would use adjuvants that have already been federally licensed for use in food animals, instead of the experimental or nonapproved adjuvants currently in use, or use no adjuvants at all. The remote delivery system would in some manner mark the animal as well as inoculate it, so that it could be distinguished from untreated animals. The ZP antigen itself would be readily available in large and inexpensive quantities,which suggests the need for genetically-engineered or synthetic forms. Current research addressing these goals is described below.

A One-Inoculation Vaccine

The current vaccine requires animals to be treated twice before full effectiveness is achieved, with the second vaccination being administered a few weeks before the onset of the breeding season. However, it is quite difficult to treat individual wild animals twice, and the time just prior to the breeding season is not always the most practical time for administering treatments. Consequently, research is focusing on the development and testing of a longer-acting one-inoculation vaccine.

The first approach to a one-inoculation vaccine used microspheres formed from a lactide-glycolide polymer that is biodegradable after injection and nontoxic as it breaks down (Kreeger 1997; Turner et al. 1997). These microspheres can be engineered to release the incorporated vaccine at varying rates by means of altering the size of the spheres and the ratio of lactide to glycolide (Eldridge et al. 1989). In the first experiment with these microspheres, in wild horses in Nevada, a single inoculation achieved the same degree of contraception as two inoculations of the raw vaccine. However, the spheres clogged syringes, needles, and darts, and delivery was impractical (Turner et al. 2001). This led to experiments with small pellets, made of the same material but shaped to fit into the needle of a dart. When the pellets are injected into the muscle of the animal, along with a bolus of raw vaccine and adjuvant, they begin to erode, releasing the vaccine at one and three months. In an initial study with the pellets, antibody titers in domestic mares remained at contraceptive lev-

els for close to a year, and in a small pilot study with wild mares, significant contraception was achieved (Liu and Turner, personal communication). Additional research is being carried out in an attempt to develop pellets that will release at nine months, thereby permitting two years of contraception from a single inoculation.

A second approach involves the packaging of the PZP vaccine in liposomes, which are formed from phospholipids and cholesterol in saline (Brown et al. 1997a). This preparation, which is being tested under the name SpayVac™ (NuTech, Halifax, Canada), has shown especially promising results for gray seals *(Halichoerus grypus)*, some of which remained infertile for at least six years after a single dose (Brown et al. 1996, 1997b). Published data concerning the effects of SpayVac in other species are limited at this time, but there is considerable interest in further testing, which is under way.

PZP, Adjuvants, and the Immune System

The PZP vaccine works in most mammalian species because the ZP molecule is similar, but not identical, among many species. The drawback to this similarity across species is that PZP is not very good at causing antibodies to be formed. Thus, it must be given with a general immunostimulant known as an adjuvant. The adjuvant, when given with a specific vaccine, causes the body to make greater concentrations of antibodies against the vaccine, which results in better contraception. The most effective available adjuvant, and the one employed in most previous PZP tests, is known as Freund's Complete Adjuvant (FCA). In many species, however, FCA also causes localized inflammation and tissue damage and may trigger false-positive tuberculosis tests after injection (Hanly et al. 1997). Thus, the FDA and other regulators, as well as those concerned with animal welfare, discourage its widespread use. Several new adjuvants are under study for use with the PZP vaccine, and success may lead to more-relaxed regulation of the vaccine by the FDA.

Different adjuvants may target different immune pathways, which has important implications for both the mechanism and duration of action (Weeratna et al. 2000). PZP has been assumed to work through short-term activation of the humoral immune system. However, some adjuvants appear to activate the cellular immune system, which could lead to the destruction of target tissues, such as the ovaries. Preliminary experiments suggest that conjugation of PZP to other immunogenic molecules, such as keyhole limpet hemocyanin (KLH) or tetanus toxoid, may also activate the cellular immune system.

Activation of the cellular immune system against the ZP protein could lead to irreversible sterilants, as well as more effective contraceptives. The ability to cause sterilization rather than temporary contraception may represent a huge advantage with some species in some situations, such as white-tailed deer or companion animals.

Genetically Engineered or Synthetic ZP Vaccines

Currently the PZP vaccine must be made as a natural product; the actual glycoprotein antigen is extracted from the zona pellucida of pig eggs. Production of the vaccine is very labor intensive and must rely on an adequate supply of pig ovaries from slaughterhouses. It is unlikely that any given small laboratory operation can produce more than fifteen thousand 65 μg doses per year. That level of production can probably meet demands for wild horses, zoo animals, and deer, but use in elephants (which currently requires three 600 μg doses) and companion animals (which number in the hundreds of thousands or millions) will far exceed the ability to produce the native PZP (see also the discussion of ethics, below). Thus, there is a significant need to produce a synthetic form of the vaccine.

A number of investigators have successfully cloned the protein backbone of the ZP molecules of several species (Harris et al. 1994; Prasad et al. 2000). Thus far, however, they have been unsuccessful at producing a recombinant ZP with contraceptive effects, probably because of difficulties in glycosylating this backbone. This step is essential in order to impart adequate antigenicity to the antigen. Even several large pharmaceutical companies have failed in their attempts to produce a genetically engineered form of the vaccine. Work on this project continues in several foreign companies and a number of research groups; among the most promising approaches is conjugating short sequences of the ZP antigen to tetanus toxin or other nonspecific immune-system booster (Patterson et al. 1999; but see Kaul et al. 1996).

Marking Darts, Oral Delivery, and Transmissible Vectors

The ability to treat free-roaming wildlife remotely with darts and know which animals have been treated is essential in the course of most applications in wildlife management. To this end, a dart has been developed by Pneu-dart® that inoculates the animal with vaccine and leaves a small paint or dye mark on the animal at the same time. While this would not allow long-term individual recognition, it would allow darters to discriminate between treated and untreated animals, which is all that is needed when success is measured by impact on the population. At the present time, this dart works in a fairly reliable manner but only at relatively short ranges; improvements are being pursued. The various dyes tested thus far have also fallen short of the mark. Deer in particular have a tendency to lick the dye off the injection site. More permanent, nontoxic dyes must be found that will survive attention by the target animal and persist over at least a three-to-four-week period.

Delivering contraceptives to wildlife orally, in baits, would be easier and more cost effective than darting. However, for safety and ethical reasons, both the public and regulatory agencies are likely to demand that any oral contraceptive must be species specific. This will be extremely difficult and expensive to accomplish, and little progress thus far has been made. A second problem is that the PZP vaccine (or any ZP vaccine) is protein in nature and easily destroyed by the digestive process of most animals. Needed is a delivery system that permits the undigested protein of the antigen to pass into the lymph of the target animal's gastrointestinal system. Several strategies to accomplish this are available. One is to insert a ZP vaccine into a nontransmissible bacterial or viral vector; this is the approach used for the oral rabies vaccine, which is incorporated into a *Vaccinia* (smallpox) vaccine (Bradley et al. 1997; Linhart et al. 1997; Miller 1997). Another method would be to incorporate the ZP vaccine into a microcapsule designed to be absorbed through the lymphoid tissue (or other route) in the digestive tract (Miller 1997). Until the species-specificity issue is resolved, however, solving the technical problems of oral delivery will not move the idea far toward management application.

Researchers working with the Australian government are seeking to engineer the genes for PZP and similar contraceptive molecules into transmissible, nonpathogenic viruses for use in controlling populations of introduced wildlife species such as European rabbits *(Oryctolagus cuniculus)* (Holland et al. 1997; Robinson et al. 1997). These viruses would be introduced into the wild populations, then transmitted from animal to animal without further human intervention. While the approach is scientifically feasible, controlling the spread of the vaccine would be a serious problem, and such a vaccine would raise serious safety and environmental concerns in the United States and around the world (see the discussion of ethics below).

Abortifacients

At least two research groups are seeking to administer compounds that will cause abortion in recipient animals. This has already been shown to be feasible in deer, with prostaglandin F2 delivered remotely via biobullet (DeNicola et al. 1997). By its nature, however, this method will require annual application, and a multi-year treatment will not be possible. Moreover, the social objections that will attend this method of wildlife control make it an unlikely solution to large-scale management efforts, especially if a safe and effective contraceptive is available.

Immunosterilization for Companion Animals

The invention of an immunosterilant for companion animals would be an extraordinary gift to the millions of dogs and cats worldwide who suffer and die each year for want of compassionate care and loving homes. In the United States alone, an estimated 6 to 8 million unwanted dogs and cats are euthanized in shelters each year, and countless other stray, feral, and abandoned animals live and die under the harshest conditions imaginable. Elsewhere the situation for cats and dogs is far, far, worse. There are many useful and important approaches to the problems faced by dogs and cats—most notably, educational outreach by animal shelters (in those communities that even *have* animal shelters). However, only effective population control will allow such problems to be solved through these efforts.

To be truly useful to animal shelters and others trying to control stray and feral populations, the ideal immunosterilant would require only one shot, be free of harmful or unpleasant side effects, and cause permanent sterility (although a multi-year, one-shot contraceptive vaccine might be somewhat helpful for controlling stray and feral populations). Ideally, such a sterilant should also mimic the behavioral and health effects of surgical sterilization, including reduced aggression in males and reduced incidence of ovarian cancer in females.

As noted above, a number of hormonal methods have been used successfully for contraception of dogs and cats (see "History of Wildlife Fertility Control"). Some, including megestrol acetate (Ovaban®) and Mibolerone (the synthetic androgen "Cheque"), are licensed for use as oral contraceptives on dogs and/or cats. However, behavioral and health side effects are common, and they are of no use to animal shelters or for control of stray and feral populations, since effectiveness ends soon after treatment stops.

Thus, immunological approaches may prove more fruitful, and research efforts in these fields have been accelerating. In an attempt to immunize dogs against their own LH, injections of human chorionic gonadotropin (hCG) were administered (Al-Kafawi et al. 1974). This experiment failed because canine LH did not crossreact with anti-hCG antibodies. An immunological approach to fertility control was also attempted in cats (Chan et al. 1981). Feline ovaries were homogenized and used to raise rabbit antibodies against the protein fractions. The antibodies, when administered to pregnant cats, caused some fetal resorption, but the results were discouraging. As in dogs, nonspecificity of the antibody appeared to be the cause of failure.

In a different immunological approach, male dogs were immunized against their own GnRH (gonadotropin releasing hormone) with GnRH conjugated to human serum globulin or tetanus toxoid (Hassan et al. 1985; Ladd et al. 1994). Plasma testosterone, LH, and sperm counts were all depressed; however, the effect was reversed when antibody levels dropped. A GnRH vaccine would have several important advantages. First, it should work on both sexes. Second, it could convey the same benefits as surgical sterilization, including loss of libido and estrus, reduction of aggressive

behavior, and reduced incidence of reproductive tract cancers.

Another promising approach to dog contraception/sterilization is immunization with the PZP vaccine (Mahi-Brown et al. 1985, 1988). Small and infrequent doses of the PZP vaccine appeared to cause cellular-mediated immune responses in bitches and led to a longer-term infertility. Long-term studies were not carried out, but in the short term this cellular immune response was associated with histologic alterations of the ovaries. Concerns about potential pathologies would have to be resolved before this approach could be considered safe (Mahi-Brown et al. 1988). Some of these concerns might be resolved by use of a more highly purified PZP preparation than was used in these studies. As mentioned above, careful selection of recombinant ZP peptides should allow a more targeted immune response and help resolve these concerns (Paterson et al. 1999; Prasad et al. 2000).

Culture, Regulations, and Politics

Immunocontraception faces a variety of technical, cultural, regulatory, and political obstacles before it will be used as a tool for management of free-ranging wildlife. The technical issues have already been discussed: what is needed is a safe, effective, one-shot, multi-year vaccine that can be delivered remotely to wildlife under field conditions. In some ways, however, the technical obstacles are the least significant.

In our view, the single most formidable barrier to the adoption of immunocontraception as a wildlife management tool is the entrenched culture of wildlife use. In the United States, this culture is most evident in the wildlife management establishment, which includes the state wildlife management agencies, much of the U.S. Fish and Wildlife Service, the hunting community, the arms and archery manufacturers, the trapping and fur industries, and the other commercial interests that profit directly or indirectly from the killing of wildlife (Gill and Miller 1997; Hagood 1997). In this paradigm wildlife has no value or significance apart from its use. This is evident in the jargon of the culture: deer are the "deer resource"; beavers and otters are "fur bearers"; wildlife is divided into "game" and "nongame" species; ending an animal's life is "harvesting."

In a culture of use, contraception of "game" animals is illogical: why prevent animal births when you can instead stimulate births and "harvest" a surplus for human use? A choice to contracept rather than kill also introduces into wildlife management a new moral dimension disconcerting to those who think in terms of exploitation: that each individual animal has a claim on the world and on us, a claim to its own life. Recognizing this claim collapses the jargon of "harvest" and "resource" and undermines the paradigm of use that it supports.

The moral challenge that wildlife immunocontraception poses to the culture of use is, in our view, the only possible explanation for the extraordinary antipathy wildlife immunocontraception has generated in state wildlife agencies and the hunting community. It is certainly not the threat that the technology itself poses to hunting; immunocontraception, at least the dart-delivered kind, is not and will not be an effective management tool in the environments in which most recreational hunting occurs (Kirkpatrick and Turner 1995).

But the antipathy is unmistakable. Almost every attempt to get a state permit to conduct an immunocontraception field study on deer has exploded into a titanic political battle, with the state agencies often leading (or goading) the opposition. One proposed study, in Amherst, New York, was blocked by a lawsuit by Safari Club International. Another was nearly blocked by the personal intervention of several pro-hunting members of Congress. The publications of the hunting industry regularly feature articles on how immunocontraception can't work—it is too cumbersome and/or expensive, it is failing in this way or that, and of course, it is inferior to hunting in every way. One more extreme hunting newsletter featured a letter that drew parallels between our research and that of the Nazis. In community deer meetings, angry hunters stand up one after another to denounce immunocontraception as a fraud, as a threat to wildlife management and a traditional way of life, as "playing God," and as an anti-hunting plot (Kirkpatrick and Turner 1997). A national bowhunting advocacy group recently began issuing action alerts notifying its members of our public speaking engagements.

In the United States the culture of wildlife use is waning, especially in the cities and suburbs, where most people now live (Kellert 1985, 1993). Interest in and support for wildlife immunocontraception on the part of the public, the media, and some state legislatures suggests that this obstacle will be overcome.

In much of the world, however, the culture of wildlife use remains dominant and is reflected in the multi-billion-dollar worldwide trade in wildlife and wildlife parts (Freese 1998). Among people struggling to support their families and maintain human life and dignity, such attitudes are understandable, if tragic. But no such "necessity defense" can be constructed for the profiteers, the entrepreneurs from wealthy nations who make fortunes trading in wild-caught birds, bear gall bladders, and rhinoceros horn. Although the international community frowns on smuggling, the entire premise of treaties such as the Convention on International Trade in Endangered Species of Fauna and Flora (CITES) is that wildlife use is good so long as it is "sustainable."

Wildlife contraception makes little sense in that context. Why contracept elephants when you could shoot them, eat the meat, and sell the hides and tusks for great profit? The answers to that question are not simple. They ultimately rest on the morality of shoot-

ing elephants and the long-term economic, social, and spiritual advantages of treating these and other wild creatures with respect and compassion. But the question will have to be answered, and answered convincingly, before immunocontraception can be widely applied to elephants and other locally overabundant wildlife throughout the world.

Regulatory and Practical Issues

Several specific regulatory and practical issues will have to be addressed and resolved before PZP or other immunocontraceptives become mainstream management tools.

Within the United States, the most important regulatory barrier is approval by the Center for Veterinary Medicine of the U.S. Food and Drug Administration (FDA). The FDA has little experience with animal vaccines. Most animal vaccines are regulated by the U.S. Department of Agriculture (USDA), but the USDA's authorizing legislation only permits it to regulate vaccines for disease prevention. Since pregnancy is not considered a disease, regulatory authority reverts to the FDA. Unfortunately, most of the FDA regulations and standards that apply to immunocontraception are tailored to approval of drugs, which are generally more stringently regulated and require more rigorous testing than do vaccines.

As of mid-2000, research on PZP is being carried out under the authority of Investigational New Animal Drug (INAD) files established with the FDA. (In our case, the INAD is held by The HSUS.) The INAD file is the heart of a process designed to control development and testing of new animal drugs and vaccines and guide acceptable products toward eventual FDA approval for marketing and commercial distribution. Fundamentally, the FDA asks this question when considering a product for approval: Is the specific product safe and effective for its intended purpose if used as directed? The question is asked comprehensively; it extends to manufacturing, storage, packaging, means and schedule of delivery, animals targeted, and labeling of the vaccine or drug. These will be high hurdles for PZP or any contraceptive vaccine (especially a recombinant form) or drug to overcome. But it can be done, and eventually it will be done for a safe, effective wildlife contraceptive.

Since management of wildlife in the United States is carried out under state authority (with some exceptions on federal land), applying immunocontraceptives to free-ranging wildlife will generally require permits from state wildlife agencies (Messmer et al. 1997). Many will yield such permits only slowly and grudgingly. However, as the novelty of the technique wears off, as its limitations and successes are demonstrated in field studies, as a safety record is accumulated, and as FDA concerns are met, state agencies will become more comfortable with immunocontraception techniques. Some progress has already been made, at least in the agencies' rhetoric. While in the early 1990s the response of state agencies to deer contraception was "no, not now, not ever," by the close of the decade many state agency personnel were conceding that PZP does at least stop deer from breeding, and they began to speak of contraception as an important tool for future management efforts. Given the scope and seriousness of public concerns over deer and other wildlife, it is inconceivable that state agencies could resist indefinitely public demands for a humane, nonlethal tool that could help solve at least some conflicts with deer.

The practical issues include determining who will pay for wildlife contraception and who will carry it out. State agencies are uniquely unsuited to pay for or conduct wildlife management through immunocontraception. They have neither the money nor the personnel (a situation that certainly aggravates agency worries over the potential spread of immunocontraception as a management tool). The resources they do have are generated principally by hunters, who repeatedly and loudly voice their objections to having their license fees spent on contraception. State legislatures have become accustomed to state wildlife agencies generating their own funds and depending on hunters to conduct management activities. They are extremely reluctant to start diverting general revenues to these otherwise self-supporting agencies. Although some immunocontraception studies have received state funding and support (notably in New York and Connecticut), the prospects for state wildlife agencies getting any money to conduct immunocontraception management programs in the field are very limited.

If state agencies do not fund and conduct these programs, who will? We believe the answers are already beginning to emerge. Generally, HSUS immunocontraception studies have been funded at least in part by land owners, land management agencies, and communities in which the studies occur. The wild-horse contraception projects at Assateague Island and Cape Lookout National Seashores are being funded and carried out by the National Park Service, which is also involved in supporting and carrying out the deer project at Fire Island National Seashore and the Tule elk project at Point Reyes National Seashore. Wild-horse contraception studies on western public lands have been cooperative efforts of The HSUS, the research team, and the Bureau of Land Management; over time, the BLM is increasing its responsibility for carrying out these programs. NIST, part of the U.S. Department of Commerce, is jointly undertaking a deer contraception study with The HSUS on the NIST campus in Maryland. The U.S. Navy is implementing fertility control of water buffalo on Guam. Local agencies, such as Columbus-Franklin County Metro Parks, in Ohio, and Morris County Parks, in New Jersey, have also taken lead roles in conducting deer immunocontraception studies on their own properties. At Fire Island and in Groton, Connecticut, funding has been provided by local communities and residents.

Deer management, in particular, is increasingly being carried out at the local level. Confronted with increasing numbers of deer-human conflicts, town councils, county governments, park commissions, and other municipal bodies have developed deer-management plans and employed city police, animal control officers, volunteer hunters, and private contractors to carry them out. This localization has been formally recognized in Maryland, where the state deer-management plan emphasizes local needs and preferences, and in New Jersey, where recently approved legislation establishes community-based deer management plans. These plans would be developed locally by county and municipal governments, submitted to the state divisions of fish, game, and wildlife for review and approval, and carried out by either government personnel or private contractors. While the emphasis of these plans clearly now rests on killing, fertility control is explicitly recognized in the New Jersey legislation as a local management alternative.

We envision that immunocontraception projects (indeed, all urban wildlife management) eventually will be funded locally, carried out by local government personnel or private contractors, and regulated by the states, which will establish policies, issue permits, oversee research, and certify private contractors and other practitioners.

The Ethics of Immunocontraception

Ethical questions concerning the application of immunocontraception to wildlife have been raised by people expressing a wide spectrum of viewpoints, from sport hunters to hardline animal rights advocates. We choose to take a pragmatic approach. When immunocontraception is considered, it will be considered as one of several management alternatives, and so to each of the questions posed below must be added the implicit question, "compared to what?" (Oojges 1997; Singer 1997).

Is it right to manipulate a wild animal's reproductive system, and potentially its behavior, for human purposes? All other things being equal, our ethical and esthetic preference would be simply to leave wildlife alone. We recognize the intrinsic right of all wild creatures to live out their lives unmanipulated by humans, and we personally take great pleasure in observing and participating in the continuing and ever-surprising story of life on earth. But the lives of many wild creatures—especially those close to human habitation—are already subject to human manipulation, much of it deliberately or incidentally destructive. We shape the terms of animal existence by our settlement patterns; engineering of land and water; discharging of the byproducts of human life into the rivers, oceans, and atmosphere; and invasion of almost every corner of the planet.

And as a practical matter, leaving them alone is not always a choice we have. The public demands that action be taken when public health, safety, or subsistence are threatened by wildlife. Not only is this view ethically defensible, but (more to the point) it is also widespread, and we do not see this consensus changing in our lifetimes. The action taken need not be manipulation of wildlife populations; but at very high population densities, "passive" management techniques (e.g., exclusion and traffic manipulation) may be insufficient to resolve public concerns. Alternatives typically considered include some form of public hunting, sharpshooting, capture and relocation or slaughter, or other actions that are lethal, cruel, or both. In comparison to those alternatives, immunocontraception appears to be a fairly gentle population manipulation.

Isn't immunocontraception unnatural? Many sport hunters feel that they fill the ecological niche vacated by the natural predators that have been eliminated from the landscape and that hunting is therefore a natural activity. (Some take this further, asserting that humans are hunters by nature and that hunting fulfills some biological imperative.) To this role they contrast immunocontraception, which they dub "unnatural" and "playing God."

A strong case can be made that sport hunting is not natural. The use of all-terrain vehicles, laser sights, GPS units, and other twenty-first-century gadgets and gizmos is not natural, nor are the pervasive population, behavioral, even genetic effects of American sport hunting: the focus on trophy animals, the likely disruption of normal social organization, the distortion of normal population age and sex structures. Sport hunter (or predator) populations are not regulated by game (or prey) populations, as they would be in nature. Although the population, behavioral, and genetic effects of immunocontraception are not yet fully known, they are unlikely ever to achieve the profound and unnatural impacts of sport hunting.

Is it right to kill pigs (to make PZP) to save deer and horses? No. PZP is produced from the ovaries of pigs purchased from slaughterhouses. If we believed that more pigs were dying because we were making PZP, we would stop. More than 100 million pigs are killed in slaughterhouses each year, and we cannot believe that PZP research has any impact on that total. Nevertheless, this consideration adds urgency to the search for a synthetic form of the vaccine, especially if a form of ZP should ever prove applicable to companion animals. In that case, the commercial production of millions of doses per year might actually affect the market for dead pigs, and extraction of PZP from pigs on that scale would be ethically unacceptable to us.

Would it ever be appropriate to use oral contraceptives or transmissible contraceptives on free-ranging wildlife? Oral contraceptives for wildlife, packaged in attractive baits, would certainly make vaccine delivery easier and cheaper. Consequently, they would broaden the range of potential applications. This could be good or bad. We would consider it desirable if

contraceptives could replace noxious lethal controls with minimal behavioral and ecological effects. Like poison baits and pesticides, however, oral contraceptives offer many opportunities for abuse. Rather than the careful and limited application that dart delivery forces on our current use of immunocontraceptives, oral contraceptives could be scattered incautiously and indiscriminately, leading to unpredictable biological effects on a large scale. These risks are amplified if the immunocontraceptives are not species specific.

The subject of transmissible contraceptives is even more complex. In his 1985 novel *Galapagos,* Kurt Vonnegut describes a world in which the human population is driven nearly to extinction by a virus that sweeps across the planet rendering its human hosts infertile (except for a small group isolated on the Galapagos Islands, where the plot then unfolds). This is the deepest fear engendered by the concept of transmissible contraceptives—that once released, such an agent could not be controlled and its unanticipated effects could be catastrophic for the target species, for nontarget species, and even for our own species. We believe that there would be absolutely no support in the United States for release of such an agent: no wildlife overabundance problem with which we are presently coping could justify even considering assuming that level of risk.

In Australia, where much of the research on transmissible immunocontraceptives is being conducted, a different story line is unfolding. The introduction and phenomenal prosperity of European rabbits, red foxes, domestic cats, and house mice has devastated dozens of native marsupial species in a true ecological catastrophe. Australia's response has been to kill these once-welcomed invaders by the millions with poison, traps, guns, blasting, gas, disease, and every other cruel, destructive device imaginable. That animal welfare catastrophe, in conjunction with the ecological catastrophe, has led animal protection groups in Australia to support (with conditions) the ongoing research into transmissible immunocontraceptives (Oojges 1997). But because the risks of releasing such agents would extend beyond Australia, a clash between Australians and the rest of the world might be anticipated, even among animal protectionists.

Conclusion

In spite of the frustrations and obstacles—personal, political, and bureaucratic—we remain optimistic about the future of wildlife contraception. It may be that we are simply optimistic people, but our optimism draws support from our experience. One of us (JFK) has been working on wildlife fertility control for almost thirty years and the other (ATR), for just under a decade; we have seen progress. Operationally, we've progressed in thirty years from capture, field surgery, and implantation with gobs of physiologically and environmentally suspect steroids to darting animals in the field at a distance of twenty-five to fifty yards with one-fifth of a teaspoon of biodegradable vaccine. In the public's eyes, wildlife contraception has gone from a joke to a pretty darned good idea, "if you can make it work." Even in the deer meetings we've survived (Kirkpatrick and Turner 1997; Rutberg 1997), after all the shouting, blustering, posturing, and accusing is over, there's usually someone who takes us aside and says, "You know, these animals really are a problem, but it's not right to kill them, so if you could find another way to control them it would make people really, really, happy."

For the animals—the old mares on Assateague, the old does on Fire Island, and the rest—and for those people in the back of the room, we should all be working to find that other way.

Notes

[1]These attitudes still linger, and many of these species, such as gray wolves and grizzly bears, still confront them in their path to recovery.

[2]Dart delivery systems have changed dramatically in the past twenty-five years and have improved significantly the ability to treat free-roaming animals at greater ranges; thus, dart-delivered drugs were not an early priority for scientists looking into this field.

Literature Cited

Al-Kafawi, A.A., M.L. Hopwood, M.H. Pineda, and L.C. Faulkner. 1974. Immunization of dogs against human chorionic gonadotropin. *American Journal of Veterinary Research* 35: 261–64.

Allen, S.H. 1982. Bait consumption and diethylstilbestrol influence on North Dakota red fox reproductive performance. *Wildlife Society Bulletin* 10: 370–74.

Balser, D.C. 1964. Management of predator populations with antifertility agents. *Journal of Wildlife Management* 28: 352–58.

Barber, M.R., and R.A. Fayrer-Hosken. 2000. Evaluation of somatic and reproductive immunotoxic effects of the porcine zona pellucida vaccination. *Journal of Experimental Zoology* 286: 641–46.

Barfneet, C.F., and H.C. Peng. 1968. Antifertility factors from plants. I. Preliminary extraction and screening. *Journal of Pharmaceutical Sciences* 57: 1607–08.

Becker, S.E., and L.S. Katz. 1997. Gonadatropin-releasing hormone (GnRH) analogs or active immunization against GnRH to control fertility in wildlife. Pp. 11–19 in *Contraception in wildlife management,* ed. T. J. Kreeger. USDA/APHIS Technical Bulletin No. 1853.

Bell, R.L., and T.J. Peterle. 1975. Hormone implants control reproduction in white–tailed deer. *Wildlife Society Bulletin* 3: 152–56.

Bell, M., C. A. Daley, S. L. Berry, and T. E. Adams. 1997. Pregnancy status and feedlot performance of beef heifers actively immunized against gonadatropin-releasing hormone. *Journal of Animal Science* 75: 1185–89.

Berger, P.J., E.H. Sanders, P.D. Gardner, and N.C. Negus. 1977. Phenolic plant compounds functioning as reproductive inhibitors in *Microtus montanus. Science* 195: 575–77.

Bickle, C.A., J.F. Kirkpatrick, and J.W. Turner Jr. 1991. Contraception in striped skunks with Norplant® implants. *Wildlife Society Bulletin* 19: 334–38.

Bradley, M.P., L.A. Hinds, and P.H. Bird. 1997. A bait-delivered immunocontraceptive for the European red fox *(Vulpes vulpes)* by the year 2002? *Reproduction, Fertility, and Development* 9: 111–16.

Brown, R.G., W.D. Bowen, J.D. Eddington, W.C. Kimmins, M. Mezei, J.L. Parsons, and B. Pohajdak. 1997a. Temporal trends in antibody production in captive grey, harp, and hooded seals to a single administration immunocontraception vaccine. *Journal of Reproductive Immunology* 35: 53–64.

————. 1997b. Evidence for a long-lasting single administration contraceptive vaccine in wild grey seals. *Journal of Reproductive Immunology* 35: 43–51.

Brown, R.G., W.C. Kimmins, M. Mezei, J.L. Parsons, B. Pohajdak, and W.D. Bowen. 1996. Birth control for grey seals. *Nature* 379: 30–31.

Brushman, H.H., S.B. Linhart, D.S. Balser, and L.W. Sparks. 1967. A technique for producing anti-fertility tallow baits for predator mammals. *Journal of Wildlife Management* 32: 183–84.

Buergelt, C.P., and G.V. Kollias. 1987. Proliferative disease in the uterus of two large Felidae receiving melengestrol acetate. Proceedings of the Thirty-fourth Annual Meeting of the Amerocan College of Veterinary Pathology, Monterey, California (Abstract).

Burke, T. 1977. Fertility control in the cat. *Veterinary Clinics of North America* 7: 699–703.

Chan, S.W.Y., D.E. Wildt, and P.K. Chakraborty. 1981. Development and characterization of feline ovarian antiserum. *American Journal of Veterinary Research* 42: 1322–27.

Cheatum, E.L. 1967. Rabies control by inhibition of fox reproduction. Doctoral dissertation. Ithaca, N.Y.: Cornell University.

Conover, M.R. 1997. Monetary and intangible valuation of deer in the United States. *Wildlife Society Bulletin* 25: 298–305.

Cranston, L. 1945. The effect of Lithospermum ruderale on the estrus cycle in mice. *Journal of Pharmacology and Experimental Therapeutics* 83: 130–42.

Daels, P.F., and J.P. Hughes. 1995. Fertility control using intrauterine devices: An alternative for population control in horses. *Theriogenology* 44: 629–39.

Davis, D.E. 1959. Effects of triethylenemelamine on testes of starlings. *Anatomical Record* 134: 549–53.

————. 1962. Gross effects of triethylenemelamine on gonads of starlings. *Anatomical Record* 142: 353–57.

DeNicola, A.J., D.J. Kessler, and R.K. Swihart. 1997. Remotely delivered prostaglandin F2 implants terminate pregnancy in white-tailed deer. *Wildlife Society Bulletin* 23: 527–31.

Dunlap, T.R. 1988. *Saving America's wildlife*. Princeton, N.J.: Princeton University Press.

Elder, W.H. 1964. Chemical inhibition of ovulation in the pigeon. *Journal of Wildlife Management* 28: 556–75.

Eldridge, J.H., R.M. Gilly, J.K. Stass, Z. Moldozeanu, J.K. Muelbroek, and T.R. Tice. 1989. Biodegradable microcapsules: vaccine delivery systems for oral immunization. *Current Topics in Microbiology and Immunology* 146: 59–66.

Farnsworth, N.R., and D.P. Waller. 1982. Current status of plant products reported to inhibit sperm. *Research Frontiers in Fertility Regulation* 2: 1–16.

Fayrer-Hosken, R.A., P. Brooks, H. Bertschinger, J.F. Kirkpatrick, J.W. Turner Jr., and I.K.M. Liu. 1997. Management of African elephant populations by immunocontraception. *Wildlife Society Bulletin* 25: 18–21.

Florman, P.M., and H.M. Wassarman. 1985. Olinked oligosaccharides of mouse egg ZP3 account for its sperm receptor activity. *Cell* 41: 313–24.

Fraser, H.M., J. Sandow, H. Seidel, and W. von Rechenberg. 1987. An implant of a gonadotropin releasing hormone agonist (buserelin) which suppresses ovarian function in the macaque for 3–5 months. *ACTA Endocrinologica* 115: 521–27.

Freese, C.H. 1998. *Wild species as commodities*. Washington, D.C.: Island Press.

Frisbie, K., and J.F. Kirkpatrick. 1998. Immunocontraception of captive species. A new approach to population management. *Animal Keeper's Forum* 25: 346–50.

Garrett, M.G., and W.L. Franklin. 1983. Diethylstilbestrol as a temporary chemosterilent to control black-tailed prairie dog populations. *Journal of Range Management* 36: 753–56.

Gilbert, F.F., and D.G. Dodds. 1992. *The philosophy and practice of wildlife management.* 2nd edition. Malabar, Fla.: Krieger Publishing Co.

Gill, R.B., and M.W. Miller. 1997. Thunder in the distance: The emerging policy debate over wildlife contraception. Pp. 257–67 in *Contraception in wildlife management,* ed. T.J. Kreeger. USDA/APHIS Technical Bulletin No. 1853.

Greer, K.R., W.H. Hawkins, and J.E. Catlin. 1968. Experimental studies of controlled reproduction in elk (Wapiti). *Journal of Wildlife Management* 32: 368–76.

Hagood, S. 1997. State wildlife management: The pervasive influence of hunters, hunting, culture, and money. Washington, D.C.: The Humane Society of the United States.

Hanly, W.C., B.T. Bennett, and J.E. Artwohl. 1997. Overview of adjuvants. Pp. 1–8 in *Information resources for adjuvants and antibody production: Comparisons and alternative technologies 1990-97*, ed. C.P. Smith. Beltsville, Md.: National Agricultural Library, USDA/ARS.

Harder, J.D. 1971. The application of an antifertility agent in the control of a white-tailed deer population. Doctoral dissertation. Ann Arbor: University of Michigan.

Harder, J.D., and T.J. Peterle. 1974. Effects of diethylstilbestrol on reproductive performance in white-tailed deer. *Journal of Wildlife Management* 38: 183–96.

Harris, J.D., D.W. Hibler, G.K. Fontenot, K.T. Hsu, E.C. Yurewicz, and A.G. Sacco. 1994. [sic] Cloning and characterization of zona pellucida genes and cDNA's from a variety of mammalian species: The ZPA, ZPB, and ZPC gene families. *DNA Sequencing* 4: 361–93.

Hassan, T., R.E. Falvo, V. Chandrashekar, B.D. Schanbacher, and C. Awoniyi. 1985. Active immunization against LHRH in the male mongrel dog. *Biology of Reproduction* 32 (Suppl. 1): 222.

Heilmann, T.J., R.A. Garrott, L.L. Cadwell, and B.L. Tiller. 1998. Behavioral response of free-ranging elk treated with an immunocontraceptive vaccine. *Journal of Wildlife Management* 62: 243–50.

Herr, J., D.J. Conklin, and R.S. McGee. 1989. Purification of low molecular weight forms of seminal vesicle antigen by immunoaffinity chromatography on bound monoclonal antibody MHS 5. *Journal of Reproductive Immunology* 16: 99–113.

Holland, M.K., J. Andrews, H. Clarke, C. Walton, and L.A. Hinds. 1997. Selection of antigens for use in a virus vectored immunocontraceptive vaccine: PH-20 as a case study. *Reproduction, Fertility, and Development* 9: 117–24.

Howard, W.E., and R.E. Marsh. 1969. Mestranol as a reproductive inhibitor in rats and voles. *Journal of Wildlife Management* 33: 403–08.

Inaba, T., T. Umehara, J. Mori, R. Torii, H. Tamada, and T. Sawada. 1996. Reversible suppression of pituitary-testicular function by a sustained release formulation of a GnRH agonist (leuprolide acetate) in dogs. *Theriogenology* 46: 671–77.

Kaul, R., A. Afzalpurkar, and S.K. Gupta. 1996. Strategies for designing an immunocontraceptive vaccine based on zona pellucida synthetic peptides and recombinant antigen. *Journal of Reproduction and Fertility* (Supplements 50): 127–34.

Kellert, S.R. 1985. Historical trends in perceptions and uses of animals in twentieth-century America. *Environmental Review* 9: 19–33.

————. 1993. Public view of deer management. Pp. 8–11 in *Deer management in an urbanizing region,* ed. R.L. Donald. Washington, D.C.: The Humane Society of the United States.

Kirkpatrick, J.F. 1995. Management of wild horses by fertility control: The Assateague experience. National Park Service (NPS) Scientific Monograph. Denver, Co.: NPS.

Kirkpatrick, J.F., and J.W. Turner Jr. 1985. Chemical fertility control and wildlife management. *Bioscience* 35: 485–91.

————. 1987. Chemical fertility control and the management of the Assateague feral ponies. Final Report, NPS contract CA 1600-30005, Assateague Island National Seashore, Berlin, MD.

————. 1991. Reversible fertility control in nondomestic animals. *Journal of Zoo and Wildlife Medicine* 22: 392–408.

————. 1995. Urban deer fertility control: Scientific, social, and political issues. *Northeast Wildlife* 52: 103–16.

————. 1997. Urban deer contraception: The seven stages of grief. *Wildlife Society Bulletin* 25: 515–19.

Kirkpatrick, J.F., J.W. Turner Jr., and A. Perkins. 1982. Reversible fertility control in feral horses. *Journal of Equine Veterinary Science* 2: 114–18.

Kirkpatrick, J.F., I.K.M. Liu, and J.W. Turner Jr. 1990. Remotely-delivered immunocontraception in feral horses. *Wildlife Society Bulletin* 18: 326–30.

Kirkpatrick, J.F., I.K.M. Liu, J.W. Turner Jr., and M. Bernoco. 1991. Antigen recognition in feral mares previously immunized with porcine zonae pellucidae. *Journal of Reproduction and Fertility* (Supplements 44): 321–25.

Kirkpatrick, J.F., I.K.M. Liu, J.W. Turner Jr., R. Naugle, and R. Keiper. 1992. Long-term effects of porcine zonae pellucidae immunocontraception on ovarian function of feral horses (Equus caballus). *Journal of Reproduction and Fertility* 94: 437–44.

Kirkpatrick, J.F., R.Naugle, I.K.M. Liu, J.W. Turner Jr. 1995a. Effects of seven consecutive years of porcine zona pellucida contraception on ovarian function in feral mares. *Biology of Reproduction* Monograph Series 1: Equine Reproduction VI. 411–18.

Kirkpatrick, J.F., W. Zimmermann, L. Kolter, I.K.M. Liu, and J.W. Turner Jr. 1995b. Immunocontraception of captive exotic species. I. Przewalski's horse (Equus przewalski) and banteng (Bos javanicus). *Zoo Biology* 14: 403–16.

Kirkpatrick, J.F., I.K.M. Liu, and J.W. Turner Jr. 1996a. Contraception of wild and feral equids. Pp. 161–69 in *Contraception in wildlife management,* ed. T.J. Kreeger. Washington, D.C.: U.S. Government Printing Office.

Kirkpatrick, J.F., P.P. Calle, P. Kalk, I.K.M. Liu, and J.W. Turner Jr. 1996b. Immunocontraception of captive exotic species. II. Formosa sika deer (Cervus nippon taiouanus), Axis deer (Cervus axis), Himalayan tahr (Hemitragus jemlahicus), Roosevelt elk (Cervus elaphus roosevelti), Reeve's Muntjac (Muntiacus reevesi), and sambar deer (Cervus unicolor). *Journal of Zoo and Wildlife Medicine* 27: 482–95.

Kirkpatrick, J.F., J.W. Turner Jr., I.K.M. Liu, R.A. Fayrer-Hosken, and A. Rutberg. 1997. Case studies in wildlife immunocontraception: Wild and feral equids and white-tailed deer. *Reproduction, Fertility, and Development* 9: 105–10.

Kreeger, T.J. 1997. Overview of delivery systems for the administration of contraceptives to wildlife. Pp. 29–48 in *Contraception in wildlife management,* ed. T.J. Kreeger. USDA/APHIS Technical Bulletin No. 1853.

Ladd, A., G. Prabhu, Y.Y. Tsong, T. Probst, W. Chung, and R.B. Thau. 1988. Active immunization against gonadotropin-releasing hormone combined with androgen supplementation is a promising antifertility vaccine for males. *American Journal of Reproductive Immunology and Microbiology* 17: 121–27.

Ladd, A., Y.Y. Tsong, G. Prabhu, and R. Thau. 1989. Effects of long-term immunization against LHRH and androgen treatment on gonadal function. *Journal of Reproductive Immunology* 15: 85–101.

Ladd, A., Y.Y. Tsong, A.M. Walfield, and R. Thau. 1994. Development of an antifertility vaccine for pets based on active immunization against luteinizing hormone-releasing hormone. *Biology of Reproduction* 51: 1076–83.

Levenson, T. 1984. Family planning for deer. *Discover* Dec.:35–38.

Linhart, S.B., and R.K. Enders. 1964. Some effects of diethylstilbestrol in captive red foxes. *Journal of Wildlife Management* 28: 358–63.

Linhart, S.B., A. Kappeler, and L.A. Windberg. 1997. A review of baits and bait delivery systems for free-ranging carnivores and ungulates. Pp. 69–132 in *Contraception in wildlife management,* ed. T.J. Kreeger. USDA/APHIS Technical Bulletin No. 1853.

Liu, I.K.M., M. Bernoco, and M. Feldman. 1989. Contraception in mares heteroimmunized with porcine zona pellucida. *Journal of Reproduction and Fertility* 85: 19–29.

McShea, W.J., S.L. Monfort, S. Hakim, J. Kirkpatrick, I. Liu, J.W. Turner Jr., L. Chassy, and L. Munson. 1997. The effect of immunocontraception on the behavior and reproduction of white-tailed deer. *Journal of Wildlife Management* 61: 560–69.

Mahi-Brown, C.A., R. Yanagimachi, J.C. Hoffman, and T.T.F. Huang. 1985. Fertility control in the bitch by active immunization with porcine zonae pellucidae: Use of different adjuvants and patterns of estradiol and progesterone levels in estrous cycles. *Biology of Reproduction* 32: 761–72.

Mahi-Brown, C.A., R. Yanagimachi, M.L. Nelson, H. Yanagimachi, and N. Palumbo. 1988. Ovarian histopathology of bitches immunized with porcine zonae pellucidae. *American Journal of Reproductive Immunology and Microbiology* 18: 94–103.

Marion, J.R. 1987. Whose wildlife is it anyway? How New York's fish and game statutes, regulations, and policies endanger the environment and have disenfranchised the majority of the electorate. *Pace Environmental Law Review* 4: 401–38.

Marsh, R.E., and W.E. Howard. 1969. Evaluation of mestranol as a reproductive inhibitor of Norway rats in garbage dumps. *Journal of Wildlife Management* 33: 133–38.

Matschke, G.H. 1980. Efficacy of steroid implants in preventing pregnancy in white-tailed deer. *Journal of Wildlife Management* 44: 756–58.

Messmer, T.A., S.M. George, and L. Cornicelli. 1997. Legal considerations regarding lethal and nonlethal approaches to managing urban deer. *Wildlife Society Bulletin* 25: 424–29.

Miller, L.A. 1997. Delivery of immunocontraceptive vaccines for wildlife management. Pp. 49–58 in *Contraception in wildlife management,* ed. T.J. Kreeger. USDA/APHIS Technical Bulletin No. 1853.

Miller, L.A., B.E. Johns, and G.J. Killian. 1999. Long-term effects of PZP immunization on reproduction in white-tailed deer. *Vaccine* 18: 568–74.

Oleyar, C.M., and B.S. McGinnes. 1974. Field evaluation of diethylstilbestrol for suppressing reproduction in foxes. *Journal of Wildlife Management* 38: 101–06.

Oojges, G. 1997. Ethical aspects and dilemmas of fertility control of unwanted wildlife: An animal welfarist's perspective. *Reproduction, Fertility, and Development* 9: 163–67.

Patterson, M., M.R. Wilson, Z.A. Jennings, M. van Duin, and R.J. Aitken. 1999. Design and evaluation of a ZP3 peptide vaccine in a homologous primate model. *Molecular Human Reproduction* 5: 342–52.

Pincus, G., J. Rock, C.R. Garcia, E. Riceway, M. Paniangua, and I. Rodriguez. 1958. Fertility control with oral medication. *American Journal of Obstetrics and Gynecology* 75: 1333–46.

Plotka, E.D., and D.N. Vevea. 1990. Serum ethinylestradiol (EE2) concentrations in feral mares following hormonal contraception with homogenous silastic implants. *Biology of Reproduction* 42 (Supplement 1): 43.

Porton, I., C. Asa, and A. Baker. 1990. Survey results on the use of birth control methods in primates and carnivores in North American Zoos. Pp. 489–97 in Proceedings of the An. A.A.Z.P.A. Conference.

Prasad, S.V., S.M. Skinner, C. Carino, N. Wang, J. Cartwright, and B.S. Dunbar. 2000. Structure and function of the proteins of the mammalian zona pellucida. *Cells Tissues Organs* 166: 148–64.

Primakoff, P., W. Lathrop, L. Woolman, A. Cowan, and D. Myles. 1988. Fully effective contraception in the male and female guinea pigs immunized with the sperm protein PH20. *Nature* 335: 543–46.

Robinson, A.J., R. Jackson, P. Kerr, J. Merchant, I. Parer, and R. Pech. 1997. Progress towards using the recombinant myoma virus as a vector for fertility control in rabbits. *Reproduction, Fertility, and Development* 9: 77–84.

Rudolph, B.A., W.F. Porter, and H.B. Underwood. 2000. Evaluating immunocontraception for managing suburban white-tailed deer in Irondequoit, New York. *Journal of Wildlife Management* 64: 463–73.

Rutberg, A.T. 1997. Lessons from the urban deer battlefront: A plea for tolerance. *Wildlife Society Bulletin* 25: 520–23.

Seal, U.S., R. Barton, L. Mather, K. Oberding, E.D. Plotka, and C.W. Gray. 1976. Hormonal contraception in captive female lions (Panthera leo). *Journal of Zoo Animal Medicine* 7: 1–17.

Shao, Z.Q. 1987. Tripterygium wilfordii, a Chinese herb effective in male fertility regulation. *Contraception* 36: 335–45.

Singer, P. 1997. Neither human nor natural: Ethics and feral animals. *Reproduction, Fertility, and Development* 9:157–62.

Skinner, S.M., S.V. Prasad, T.M. Ndolo, and B.S. Dunbar. 1996. Zona pellucida antigens: Targets for contraceptive vaccines. *American Journal of Reproductive Immunology* 35: 163–74.

Sokolowski, J.H., and F. Van Ravenswaay. 1976. Effects of melengestrol acetate on reproduction in the beagle bitch. *American Journal of Veterinary Research* 37: 943–45.

Storm, G.L., and G.C. Sanderson. 1969. Effect of medroxyprogesterone acetate (Provera) on productivity in captive foxes. *Journal of Mammology.* 50: 147–49.

———. 1970. Effect of mestranol and diethystilbestrol on captive voles. *Journal of Wildlife Management* 34: 835–43.

Thiele, L.A. 1999. A field study of immunocontraception in a white-tailed deer population. Master's thesis. College Park: University of Maryland.

Tober, J.A. 1981. *Who owns the wildlife?* The political economy of conservation in nineteenth-century America. Westport, Conn.: Greenwood Press.

Turner, J.W., Jr., I.K.M. Liu, and J.F. Kirkpatrick. 1992. Remotely delivered immunocontraception in captive white-tailed deer. *Journal of Wildlife Management* 56: 154–57.

Turner, J.W. Jr., I.K.M. Liu, A.T. Rutberg, and J.F. Kirkpatrick. 1996a. Immunocontraception limits foal production in free-roaming feral horses in Nevada. *Journal of Wildlife Management* 61: 873–80.

Turner, J.W. Jr. , I.K.M. Liu, and J.F. Kirkpatrick. 1996b. Remotely delivered immunocontraception in free-roaming feral burros. *Journal of Reproduction and Fertility* 107: 31–35.

Turner, J.W. Jr., J.F. Kirkpatrick, and I.K.M. Liu. 1996c. Effectiveness, reversibility, and serum antibody titers associated with immunocontraception in captive white-tailed deer. *Journal of Wildlife Management* 60: 45–51.

Turner, J.W. Jr., J.F. Kirkpatrick, and I.K.M. Liu. 1997. Immunocontraception in white-tailed deer. Pp. 147–59 in *Contraception in wildlife management,* ed. T.J. Kreeger. USDA/APHIS Technical Bulletin No. 1853.

Turner, J.W. Jr., I.K.M. Liu, D.R. Flanagan Jr., A.T. Rutberg, and J.F. Kirkpatrick. 2001. Immunocontraception in feral horses: One inoculation provides one year of infertility. *Journal of Wildlife Management,* in press.

U.S. Fish and Wildlife Service. 1997. 1996 National survey of fishing, hunting, and wildlife-associated recreation.

Vickery, B.H., G.I. McRae, W. Briones, A. Worden, R. Seidenberg, B.D. Shanbacher, and R. Falvo. 1984. Effects of an LHRH agonist analog upon sexual function in male dogs. *Journal of Andrology* 5: 28–42.

Vickery, B.H., G.I. McRae, B.B. Roberts, A.C. Worden, and A. Bajka. 1985. Estrus suppression in the bitch with potent LHRH agonist analogs: A new approach for pet contraception. *Biology of Reproduction* 32 (Supplement 1): 106.

Walter, W.D. 2000. A field test of the PZP immunocontraceptive vaccine on a population of white-tailed deer *(Odocoileus virginianus)* in suburban Connecticut. Master's thesis. Durham: University of New Hampshire.

Weeratna, R.D., M.J. McCluskie, Y. Xu, and H.L. Davis. 2000. CpG DNA induces stronger immune responses with less toxicity than other adjuvants. *Vaccine* 18: 1755–62.

Wildt, D.E., and S.W.J. Seager. 1977. Reproduction control in dogs. *Veterinary Clinics of North America* 7: 775–87.

Wofford, J.E., and W.H. Elder. 1967. Field trials of the chemosterilant SC12937 in feral pigeon control. *Journal of Wildlife Management* 507–14.