INDUCED INFERTILITY AS A WILDLIFE MANAGEMENT TOOL

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ABSTRACT: A growing interest in nonlethal methods for population control of nuisance or damaging species of wildlife has fostered research in reducing fertility of these overabundant wildlife species. Fertility may be reduced by interfering with the fertilization of the egg (contraception) or interfering with the implantation or development of the fertilized egg (contragestion). Research using injectable porcine zona pellucida (PZP) and gonadotropin releasing hormone (GnRH) vaccines has demonstrated that several mammalian species can be contracepted, reducing fertility for several years without revaccination. However, because vaccines currently require delivery by syringe or bio-bullet, there is a need for infertility agents that can be delivered orally. Researchers are therefore considering materials that have resulted in reduced reproductive rates in the agricultural industry. Because of the cost of getting new technology approved by the FDA, materials already approved for other purposes that can be redirected for use in wildlife infertility may have a better chance of getting approved as wildlife infertility agents. Two compounds used in the broiler chicken industry have been found to reduce hatchability if given to the layer. Due to the rapid increase of Canada geese in our parks, research is ongoing with these two compounds to reduce hatchability in the Canada goose egg. Research is also underway to test a cholesterol mimic that competes with cholesterol as the parent compound for steroid synthesis. This compound could reduce fertility in both mammalian and avian species and is currently being tested in rodents. Natural plant materials such as phytoestrogens and ergot derivatives that result in reproductive losses in domestic animals should be also explored as reproductive inhibitors in overabundant species of wildlife.

KEY WORDS: fertility control, immunocontraception, immunocontragestion, population control, reproduction, vaccine, wildlife management

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INTRODUCTION

One may induce infertility by immunocontraceptive vaccines, in which one causes an animal to produce antibodies against its own reproductive hormones. The term contraceptive vaccine assumes an antibody is used to produce the infertility. However, this paper goes beyond the use of antibody induced infertility. The term "infertility agent" or "induced infertility" is used for any agent or condition which interferes with the normal reproduction capacity of the target species. This paper does not have all the answers in this area, but is designed to get the reader thinking about the possible ways of inducing infertility in the particular target species.

The most important fundamentals for success in inducing infertility in a particular species are an understanding of the reproductive behavior and physiology of that species, and selecting the most suitable infertility agent. Examples of the reproductive behaviors that need to be considered are: seasonal versus year-round breeding; type of mating system—monogamy or polygamy, multi-estrus or mon-estrus; and does the species need a specific vegetation, temperature, or landscape to be successful in reproduction. Each of these factors may affect the effectiveness of a particular infertility agent. However, a common reason these species are overabundant is that they are adaptable to multiple and changing environments, thus their populations increase in spite of a rapidly changing landscape.

Despite more than four decades of effort, research has yet to develop and implement an effective wildlife damage control program based on inhibition of reproduction of the offending animals (Kennelly and Converse 1997). Chemical contraception through the use of synthetic steroids, estrogens, and progestins (i.e., chemosterilants) was investigated during the 1960s and 1970s in coyotes (*Canis latrans*) (Balser 1964; Brusman et al. 1968), pigeons (*Columba livia*) (Woulfe 1970), red-winged blackbirds (*Agelauis phoeniceous*) (Guarino and Schafer 1974), Norway rats (*Rattus norvegicus*) (Garrison and Johns 1975), coturnix quail (*Coturnix coturnix japonica*) (Schafer et al. 1977), and white-tailed deer (*Odocoileus virginianus*) (Matschke 1977, 1980; Roughton 1979). None of these efforts have led to practical development as a wildlife management tool for various reasons, in part because the need for repetitive applications makes chemosterilents impractical in most field situations. Steroids also tend to persist in tissue, which make them unpopular from an environmental point of view. The most practical use of steroids for contraception has been the delivery of norgestomet, a very potent progesterone, by a bio-bullet (Jacobsen et al. 1995).

Immunocontraception has required at least two injections to achieve sufficient antibody titers to induce infertility. It is impractical in the field to mark and catch the same animal twice. Therefore, it is imperative that a single shot immunocontraceptive vaccine be developed. Several scientists and companies are trying to achieve this. Oral delivery of infertility vaccines is ideal for ease and cost of applying the material. However, the cost to prove that oral vaccines are safe in the environment and that they will not affect non-target species will be increased over that of the single shot vaccine.

IDEAL INFERTILITY AGENTS

1. Infertility agents should be species specific.

Ideally, all infertility techniques would be species specific. Most infertility techniques have not been species specific; this is also true with the current immunocontraceptive vaccines. The 10-mer GnRH molecule is common to all mammals and, therefore, any species specificity would have to come from the vaccine delivery. There is an avian specific GnRH, therefore, the avian species would not be affected by mammalian GnRH contraceptives. Much of species specificity in normal mammalian reproduction is related to sperm binding of the zona pellucida, yet immunizing against pig zona pellucida (PZP) results in infertility across most mammalian species. Rodent ZP is unique among mammals, therefore, PZP is not effective as a contraceptive in rodents (Miller et al. 1997b). On the positive side, rodent ZP contraceptives should not affect other non-target mammals.

2. Infertility agents should not affect non-target species.

In the absence of species specificity one needs to be concerned about effects on non-targets. The advantage of injectable vaccination is that it has little chance to affect non-target species (assuming you dart the right species). This is in contrast to an oral infertility agent that may be eaten by non-target species; therefore, the receptacle containing the bait should be designed specifically for the target animal. For example, if one wanted to contracept a female white-tailed deer, one could design a deer bait station to allow a doe to put its head between the bars but exclude the rack of a buck which, in this case, would be a non-target.

3. Infertility agent should result in little social effect on the target species.

Another expectation of fertility control is to induce infertility without affecting social behavior. This is a difficult request and may be impossible in some situations. Garrott (1995) suggested that all immunocontraception vaccines presently being studied result in some behavioral changes. Both vaccines used for inducing infertility in the white-tailed deer (GnRH and PZP) effect behavioral changes. The PZP vaccine induces multi-estrus in the white-tailed deer doe as well as in feral horses, and the GnRH vaccine prevents both the doe and buck from coming into the fall rut. On the other hand, the coyote is a monestrous animal and PZP-induced infertility should have minimal behavioral effects. GnRH could have the effect of reducing the pair bond between the coyote pair.

A human infertility vaccine using the beta chain subunit of Human Chorionic Gonadotropin (βhCG) being tested in India is a good example of a vaccine with little effect on social or sexual behavior. Before pregnancy, the uterine wall is prepared for implantation of the fertilized egg by pituitary regulated progesterone. After fertilization, the egg (now called a blastomere) secretes hCG, taking over the regulation of progesterone needed to maintain pregnancy. The vaccine-induced hCG antibody binds to the secreted hCG, preventing it from stimulating progesterone production. Without progesterone, implantation of the egg on the uterine wall is not maintained, the egg sloughs off, is reabsorbed, and pregnancy ceases (Talwar and Gaur 1987).

4. The infertility effect should be reversible.

In many cases it would be an advantage if the contraceptive effect lasted several years, yet was reversible, to decrease risk of non-target hazards and increase management options. The two current immunocontraceptive vaccines (PZP and GnRH) fit this model, and the two oral compounds (Nicarbazin and DiazaCon) being studied must be fed frequently and do not have long-lasting effects.

However, many of the overabundant species that we are trying to contracept are seasonal breeders in which these short lasting compounds may be useful. Seasonal changes such as the day-length are sensed by the eye-pineal pathway that activates the hypothalamic-pituitary axis which turns on or off the reproductive activity of the species (Figure 1).

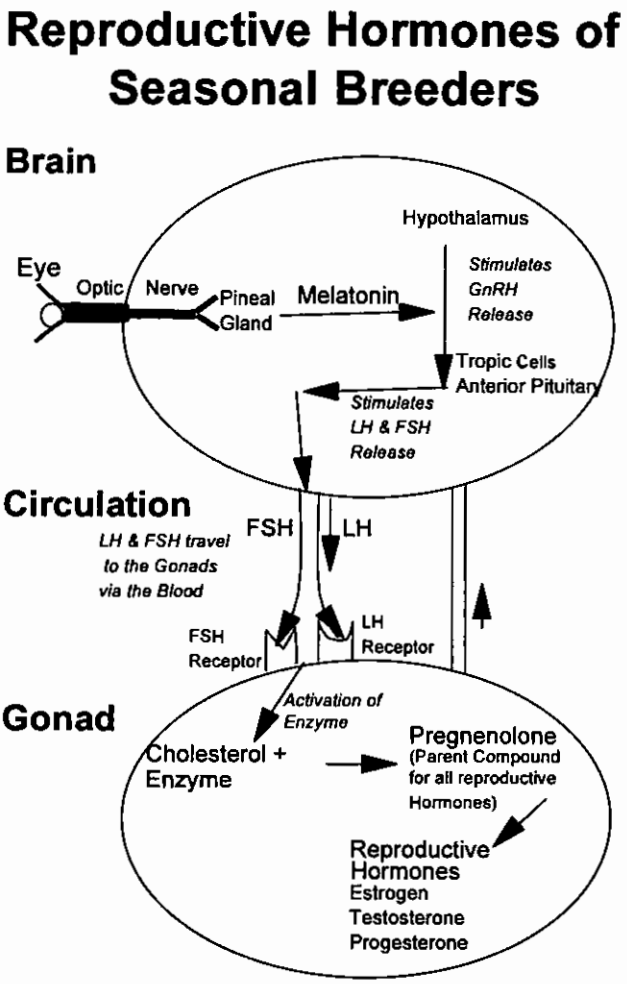

Figure 1. Reproductive hormones in seasonal breeders. The reproductive season begins when the eye senses a change in the day/night ratio. This results in a signal from the pineal gland to the hypothalamus, turning on the reproductive season.

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5. Infertility agents should be inexpensive to develop.

The cost of registering new contraceptive vaccines may prevent them from being developed commercially. Infertility agents targeting potential food species, such as deer and geese, will cost more to register then non-food species because of concerns for human safety. A company interested in developing a wildlife infertility agent must compare the developmental costs to the eventual monetary returns. The more radical the product, i.e., a recombinant bacteria delivering the contraceptive vaccine, the higher the cost for registering the product. Research currently is focusing on products already licensed by USDA or FDA for other purposes. An infertility agent that has already passed FDA scrutiny for its proposed use (such as a commercial agricultural product) and that could also be used as an infertility agent would cost less to develop than an approved product for infertility use. An example of this is the use of Nicarbazin, which is a FDA-approved agent for the control of coccidiosis in broiler chickens, but which also appears promising as a fertility control agent for pest species of birds.

CURRENT INFERTILITY METHODOLOGY

Immunocontraceptive Technology

Recent infertility research has centered around immunocontraceptive vaccines, which control fertility by stimulating the production of antibodies against gamete proteins, reproductive hormones, and other proteins essential for reproduction. These antibodies interfere with the normal physiological activity of these reproductive agents (Talwar and Gaur 1987). This approach is a natural process in the sense that antibodies induced in the target animal interfere with reproduction without the need for constant or repetitive treatment with synthetic compounds; initial treatments are effective for one to four years (Miller et al. 1999b; Turner and Kirkpatrick 1991).

Reproduction can be blocked at many sites in the reproductive process. One active area of research (Griffin 1992; Jones 1983) is use of gonadotropin releasing hormone (GnRH) immunocontraceptive vaccine to shut down the reproductive activity of both sexes by causing development of antibodies blocking GnRH and preventing the release of other essential reproductive hormones (Miller et al. 1997b)(Figure 1). Reproduction in females can be prevented by antibodies that bar sperm penetration of the zona pellucida (ZP) of an ovulated egg by binding either to the ZP or to the sperm. Embryo development can be hindered by preventing implantation and development of the fertilized egg via antibodies to GC in humans or to similar tropic hormones in other species.

Most use of immunocontraceptives has been applied to white-tailed deer (Garrott 1995) and feral horses (Turner and Kirkpatrick 1991); however, this technology could also be applied to other wildlife species such as rodents, pest species of birds, coyotes, and foxes (Miller et al. 1998).

Zona pellucida. Zona pellucida immunocontraceptives were the first to receive widespread publicity as contraceptives in deer and feral horses. Zona pellucida is an acellular glycoprotein layer located between the oocyte and the granulosa cells on the outer surface of the egg. For a sperm to fertilize the egg, it must first bind to a receptor on the ZP. An enzyme in the sperm then breaks down the ZP, allowing the sperm passage into the ovum. Antibodies to this glycoprotein layer result in infertility either by blocking the sperm from binding to and penetrating the ZP layer or by interference with oocyte maturation, leading to the death of the developing oocyte (Dunbar and Schwoebel 1988). The ZP vaccine in use today comes from the pig ovary and is called Porcine Zona Pellucida (PZP). PZP vaccine has been used to produce immunosterilization in dogs (Mahi-Brown et al.1985), baboons (Dunbar 1989), horses (Garrot et al. 1992; Kirkpatrick et al. 1990), burros (Turner et al. 1996b), coyotes (Miller 1995; Deliberto et al. 1998), and white-tailed deer (Turner et al. 1996a; Miller et al. 1999b). In the white-tailed deer study at Pennsylvania State University, we achieved 89% reduction in fawning during the two years of activity immunization. A 76% reduction in fawning was observed over the entire seven-year study (Miller et al. 1999b).

The PZP vaccine is not species specific and is effective in reducing fertility in most mammals tested. The contraceptive effect on the white-tailed doe can last several years without boosting and is reversible. PZP affects social behavior by increasing the number of times the does come into estrus, thereby prolonging the breeding season and potentially resulting in late summer or autumn fawns. Presently, the only vaccine is injectable.

Gonadotropin Releasing Hormone. GnRH as a contraceptive vaccine has been researched in domestic farm animals for over ten years. Little research has been done on GnRH as a contraceptive in wildlife species. GnRH is produced in the brain by the hypothalamus. It controls the release of the pituitary reproductive hormones, follicle stimulating hormone, and luteinizing hormone, which in turn control the functions of the ovaries and testes. Antibodies to the hypothalamic hormone will reduce the circulating level of biologically active GnRH, thereby reducing the subsequent release of reproductive hormones; the reduction or absence of these hormones leads to atrophy of the gonads and concomitant infertility of both sexes. Both avian and mammalian forms of GnRH have been identified (Sad et al. 1993; Meloen et al. 1994).

GnRH contraceptive vaccines have been evaluated as immunocastration agents in pets (Ladd et al. 1994), cattle (Adams and Adams 1992; Robertson 1982), horses (Rabb et al. 1990), sheep (Schanbacher 1982), and swine (Maloen et al.1994). Recently, in studies with Norway rats (Miller et al. 1997b), it was found that both males and females immunized with a GnRH vaccine were 100% infertile. The National Wildlife Research Center (NWRC) just finished a long-term study on the effect of GnRH on white-tailed deer in which we achieved an 86% reduction in fawning during active immunization and a 74% reduction over five years (Miller et al. 2000).

GnRH is not species specific and is effective in reducing fertility in most mammals including rodents. Its contraceptive effects last one to two years without boost and are reversible. GnRH effects social behavior by reducing the sexual activity of both sexes. It is presently available only in injectable form.

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GnRH may be a useful technique where sexual activity itself creates human/wildlife conflicts. In deer, where fall sexual activity has been associated with increased deer/car collisions, GnRH could potentially reduce the damage by reducing deer movement related to sexual activity. In cases where a pet buck has been fed in a park setting, GnRH could also reduce danger to humans during the fall rut. However, for other species reducing sexual behavior may not be advantageous; for example, GnRH could potentially reduce pair bonds in animals like coyotes (DeLiberto et al. 1998).

Sperm antibodies. Sperm head glycoproteins that bind to zona pellucida have been identified. If these glycoprotein are used as vaccines antibodies are produced in the female and are available to bind to sperm present in the oviduct, preventing conception by blocking the sperm from binding the ZP surrounding the egg. Sperm protein immunocontraception is being investigated for contraception in the red fox and the rabbit in Australia (Morell 1993; Tyndale-Biscoe 1991).

Contragestion Technology

Agents that cause the failure of the fertilized egg to implant on the uterine wall or agents that interfere with the maintenance of early pregnancy (gestation) are called contragestive agents. Agents that interfere with the maintenance of the developing embryo in late pregnancy are call abortifacients.

HCG hormone, which is produced by the implanting embryo in humans, induces the corpus luteum on the ovary to continue production of the hormone progesterone required for the maintenance of pregnancy. Antibodies to HCG reduce the bioactivity of this hormone and thereby preclude successful implantation of the fertilized egg (Stevens 1992). Contragestive vaccines induce infertility with little effect on the social and sexual behavior of the species involved. Clinical trials are underway at the National Institute of New Delhi testing a HCG vaccine to contracept fertile women (Talwar et al. 1994). Primates and horses are the only two mammals known to use CG as the key tropic reproductive hormone. It is possible that feral horse fertility, which has become a problem on Bureau of Land Management (BLM) land, could be reduced by inducing antibodies to CG.

Many species use other tropic hormones to maintain the implanted embryo, and all are probably involved with controlling the common gestational hormone progesterone. Because of apparent differences among species in tropic hormones, contragestion may provide the best possibility of species specificity. Antibodies against these tropic hormones reduce fertility by interfering with the maintenance of the uterine lining, and the egg simply sloughs off and is reabsorbed.

Progesterone is called the hormone of pregnancy. Progesterone antagonists, which can be given orally, compete for progesterone binding sites, but do not induce the biological activity needed to maintain pregnancy. These antagonists may prove valuable as orally delivered contraceptives or contragestive agents. The progesterone antagonist (which is difficult for the body to clear) can be fed monthly as a contraceptive and once in early pregnancy to interrupt pregnancy. It acts by causing a sufficient disruption in the uterine lining to prevent implantation (Gao and Short 1994).

Lutalyse, by Upjohn (PGF2α), routinely used in feedlot cattle during the first 100 days of gestation, will cause abortion within 35 days of injection. DeNicola et al. (1997) reduced fertility in white-tailed deer by injecting lutalyse. Depending on the gestational time of administration, the technology could be considered either contragestive or abortifacient. It is available only in an injectable form.

STATUS OF ORAL IMMUNOCONTRACEPTION

The most practical means to deliver a vaccine to free-roaming animals would be by oral delivery (Miller 1997a). However, oral delivery is a very difficult technology to develop and would increase the USDA and FDA regulatory involvement because it is a new and unproven technology. Although there is a great need in third world countries for oral vaccines, due to the lack of physicians to inject the vaccines, little money is currently being spent by drug companies for oral vaccine research. Much of the technology wildlife researchers use comes from human infertility studies. Therefore, one should not expect oral immunocontraception to be immediately available.

The ideal oral delivery system (mucosal immunogens) will need to have the ability to: 1) survive the acidic stomach (enteric survival); 2) be taken up into the bloodstream from the intestines (adhesion properties/ intestinal entry ability); and 3) cause a strong immune response (adjuvant and immunogenicity activity) (McGhee 1992; Mestecky 1989; Walker 1994).

Live microorganisms such as an attenuated form of *Mycobacterium bovis*, *Vibrio cholerae*, some strains of *Salmonella*, and *E. coli* have the above properties of an ideal mucosal immunogen such as mucosal adhesive properties (Attridge et al. 1997). To demonstrate the feasibility of oral vaccination in wildlife, scientists at NWRC demonstrated that white-tailed deer can be orally vaccinated successfully using a genetically-engineered *Bacillus calmette guerin* (BCG) bacterium. A good antibody response to the Osp A antigen was demonstrated after two oral doses of bacteria (Miller et al. 1999a). BCG was chosen as the vector for the antigen because of its proven performance as an oral tuberculosis vaccine in its original non-recombinant form.

Vibrio cholerae, a bacteria causing cholera, binds to intestinal epithelium through a specific receptor present in the epithelium cell wall. Cholera toxin subunit B (CTB) causes the bacteria to bind to the intestinal cell, and Cholera toxin subunit A secretes a toxin resulting in severe diarrhea. To avoid potential complications associated with live vectors, non-replicating, non-toxin producing constructs that mimic the bioadhesiveness of this organism were developed. Researchers (Alving 1986; Hornquist et al. 1994; Holmgren et al. 1993) have synthesized liposomes (lipid membranes) that incorporate bacterial receptors that allow binding to the intestinal epithelial cells. The vaccine to be delivered to the bloodstream would be encapsulated in the liposome. Scientists at NWRC designed an adhesive liposome containing GnRH immunocontraceptive to test as an oral

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immunocontraceptive in wild Norway rats. The Lipid A fraction of Lipopolysaccharide from gram-negative bacteria endotoxin was added to the liposome preparation to supplement the adjuvant effect of cholera toxin. Alving et al. (1986) found that adding microgram quantities of Lipid A to milligrams of the liposome vaccine preparation produces remarkable adjuvant properties for the lipid associated vaccine. Results from the NWRC liposome study show that 50% percent of the rats responded to the oral liposome containing GnRH vaccine. There was sufficient GnRH antibody titer in these rats to cause a significant reduction in their serum testosterone. Fifty percent of the rats did not produce an antibody titer. This type of inconsistent oral response has been found by other researchers (Miller et al. 2000).

FUTURE TECHNOLOGY TO BE EXPLORED

Natural Plant Compounds

The agriculture industry has been concerned for some time about naturally occurring plant compounds that can result in lowered reproductive rates in domestic herds. Phytoestrogens naturally occur in over 300 plant species (Shemesh and Shore 1994). Phytoestrogens exert many of the same effects as estrogen itself even though their chemical structure is quite different. It is well known that a constant source of estrogen interferes with normal cycling in most animals. Plants containing a high concentration of phytoestrogens could potentially be planted in areas of high concentrations of deer or other herbivore.

Another source of reproductive loss in cattle is endophyte-infected tall fescue. Ergot peptide alkaloids produced by the endophyte are suggested as the primary cause of the reduced reproductivity (Porter and Thompson 1991). Vasoconstrictive effects and neurohormonal imbalances are thought to be the principal mechanisms for the reproductive losses caused by these endophyte-infected grasses (Browning et al. 1998). Other natural plant toxins also have an effect on reproductive losses in the livestock industry (James et al. 1994). Where overabundant animals occur, researchers may be able to take advantage of plant estrogens and toxins to reduce reproductive rates.

INDUCED INFERTILITY AS A MANAGEMENT TOOL IN AVIAN SPECIES

Interfering with egg laying or the hatchability of the egg appears to be the best approach to reducing the reproductive capacity in birds. Egg addling, including shaking, freezing, or oiling eggs in a nest, effectively reduces egg hatchability (Pochop et al. 1998). However, this method is labor intensive and may be useful only in small-scale operations.

DiazaCon

Ornitrol (a cholesterol inhibitor) was tested in the late 1960s as an oral pigeon reproductive inhibitor. Although it was effective in reducing egg laying and egg hatchability, the pigeon is a year-round breeder, and long-term usage of the compound became expensive and had undesirable side effects on the birds, such as muscle tremors. In recent tests, NWRC scientists found the compound effective in reducing egg laying and egg hatchability up to four months in coturnix quail after feeding for ten days (Yoder 2000). This compound, 20,25 diazacholesterol, which we call DiazaCon, may be useful to control the reproduction of seasonal breeders such as the Canada goose and can be delivered orally. It is a cholesterol mimic that has a similar but not identical structure as cholesterol. DiazaCon has two possible modes of action. It may enter into the negative feedback loop inhibiting the formation of cholesterol, or it may inhibit side chain cleavage of cholesterol. In both cases, formation of pregnenolone (the parent compound of all steroid hormones) including testosterone and progesterone are reduced. DiazaCon persists in the body for a long time apparently because the side chain cannot be cleaved, preventing it from being excreted like cholesterol, so its reproductive inhibition effects can last up to several months.

DiazaCon has the potential to inhibit reproduction for an entire breeding season for some birds when fed just prior to breeding in the spring. It will affect behavior by reducing egg laying and nesting. During the fall and winter, DiazaCon would be cleared from the system, allowing birds to breed normally the next season. DiazaCon is not species specific; it can be effective in avian as well as mammalian species.

Nicarbazin

Nicarbazin (NCZ) was developed by Merck Sharp & Dohme in the 1950s as a compound that controls coccidiosis. When mixed with broiler chicken feed at .0125% it controls disease and improves weight gain and feed efficiency. The compound was found to have serious side effects if accidentally fed to breeder or layer hens, including changes in egg shell color and reduction in hatchability and egg laying, which are reversible if the compound is withdrawn. Fertilization is not affected by Nicarbazin (Hughes et al. 1991).

Feeding NCZ to laying hens produces eggs with blemished yolks. The white spots in the yolk ("yolk-mottling") can, in severe cases, give eggs the appearance of being rotten. The NCZ is incorporated into the egg yolk causing a breakdown in the yolk vitelline membrane. The white spots in the yolk probably are due to a fluid transfer of albumin from the white into the yolk via increased vitelline membrane permeability, which destroys the conditions necessary for viable development of the embryo (Jones et al. 1990).

Although not species specific, NCZ is avian specific and the infertility effect is reversible. Nicarbazin is FDA-approved for the control of coccidiosis in broiler chickens; therefore, many required toxicity studies have been done. However, before Nicarbazin can be given orally in the wild, it will have to be shown that it will not have adverse effects on non-target species. Bird behavior is not expected to be affected by this compound because the bird will lay eggs and incubate on them, but it is unlikely they will hatch. This partial hatch or non-hatch is a common process in nature for a variety of environmental reasons.

Conjugated Linoleic Acid

Conjugated Linoleic Acid (CLA) is another compound with potential to reduce avian reproduction. CLA is being used as a feed additive to increase weight gain and

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feed efficiency in broiler chickens (Chin et al. 1994). Chickens with low grade infections produce prostaglandin which stimulates a fever and muscle catabolism, resulting in weight loss of up to 10%. Linoleic acid is the parent compound for the synthesis of prostaglandin. When chickens are fed CLA, the double bonds are in the wrong position to synthesize prostaglandin. Without prostaglandin there is no weight loss associated with low grade infections, resulting in a net gain for the chicken producer (Miller et al. 1994).

Capitalizing on the weight loss concept, CLA is sold in health food stores as an antioxidant and promoted to reduce the loss of muscle in the elderly that results from low grade infections (Pariza 1993).

When CLA is fed to laying chickens, there is a loss in hatchability. The mechanism of the reduced hatchability is that CLA and 18-carbon fatty acids are incorporated into the egg yolk, which results in a solidification of the yolk at refrigerator temperatures. The conjugated double bond in CLA increases the rigidity of the fatty acid so it changes the temperature at which the yolk remains liquid (Cooney 1995). Use of CLA as a fertility control in avian species is based on the fact that in the spring, when the clutch is being laid, the bird does not incubate the nest until the clutch is complete. As the temperature drops during the night, the yolk of unprotected eggs from CLA-fed birds solidifies, interfering with the hatchability of the eggs.

CLA is specific to avian species, its infertility effect is reversible, and effects on non-targets should be minimal due to the need to feed CLA for ten or more days. It would have a minimum effect on behavior because the birds will incubate a clutch that will not hatch.

DISCUSSION

Current Infertility Agents: How Ideal Are They?

Fertility control as a wildlife management tool to reduce overabundant species should be most effective in species that are short lived with a high reproductive rate, such as rodents. Knipling and McGuire (1972) developed a theoretical model demonstrating that if 70% of male and female rats could be sterilized for three generations (one year) the entire population would be eliminated. In species such as white-tailed deer, with a low reproductive rate and a life span from 10 to 12 years, fertility control alone is not effective in reducing the population. Fertility control would be effective in maintaining a static population after the numbers have been reduced to a desired number by some other management technique.

The infertility agents we have discussed in this paper are all reversible. However, there is a large variation in the length of time that they are effective. For example, PZP immunocontraception can be effective for one to four years before the contraceptive effect is reversed. Nicarbazin is cleared within days and, therefore, the feeding period is critical to contracept a seasonal breeder.

Behavioral responses vary from total reduction of sexual function in both males and females with GnRH immunocontraceptive vaccines to failure to implant or maintain pregnancy with contragestion vaccines or agents, multiple estrus in the females immunized with ZP, or failure of the female to cycle. Multiple cycles, failure to maintain implantation of the fertilized egg, and females sitting on eggs that never hatch are all variations found in nature and should be considered minimal behavioral changes.

Immunocontraception brings a new level of safety to consumptive use of dosed wildlife that are used for food by humans and other animals. An animal that has been vaccinated contains antibodies that prevent reproduction, in addition to millions of other antibodies, all of which are harmless to the organism that digests them, just like any other proteinaceous food consisting of amino acids. Similarly, of the three infertility agents suggested for birds Nicarbazin and CLA are used routinely in chickens, and DiazaCon was initially designed to be given to humans, and therefore, should not be considered a hazard for human consumption.

Fertility control as a technology is available today, but only in laboratory studies, pen studies, and in limited field situations with small numbers of animals. Immunocontraceptive and contragestive vaccines are being produced in limited quantities, and animals injected with these vaccines become infertile for one to three years. However, to be practical for controlling free-ranging animal populations, these agents will have to be given orally. The technology for developing oral vaccines is in its infancy, but rapid progress in this field is likely because of a worldwide need for oral vaccines against diseases such as cholera (Holmgren et al. 1992; Holmgren et al. 1993; Walker 1994) and the acquired immune deficiency syndrome (AIDS) virus. Table 1 compares the properties of the infertility agents currently under study.

Species specific contraceptive vaccines continue to elude us. Scientific technology needed to identify the receptor for a particular species is in its infancy. For the present time, the vaccine delivery system is the only method of providing a species specific vaccine.

In addition to development of effective vaccines and other types of infertility agents, a host of other issues (e.g., safety, economy, delivery, large scale efficacy, ecological effects, population modeling, regulatory matters, ethics) will require close examination and resolution before contraception can become a tool available to the wildlife manager (Bomford 1990).

Public and hunter acceptability is necessary for the successful implementation of these techniques. Public forums discussing the advantages and disadvantages of these techniques would be helpful before they are taken to the field.

Warren (1995) discussed a number of the factors relevant to the practical and logistical implementation of contraceptives for controlling wildlife. He correctly pointed out that development will take a team approach involving the laboratory scientists (e.g., immunologists, molecular biologists, reproductive physiologists) who develop the contraceptive vaccines and associated technologies, and the wildlife biologists who will need to contribute to the development of delivery systems and the means to measure field efficacy and safety. Wildlife contraceptive technologies are potentially valuable as a new tool to be integrated with more traditional methods of wildlife population management.

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Table 1. Comparison of some currently available induced infertility agents.

Agent	Species Specific	Delivery Specificity	Behavior Modification	Reversible	Licensed for Other Use
GnRH Vaccine	No	Yes by Dart/ Possible Orally	Yes	Yes	No
PZP Vaccine	No	Yes by Dart/ Possible Orally	Yes	Yes	No
Nicarbazin	No	Possible Orally	Possible	Yes	Yes
Diazacon	No	Possible Orally	Possible	Yes	No
Ergot	No	Possible Orally	Possible	Yes	No
Progesterone Antagonists	No	Possible Orally	Possible	Yes	No
Conjugated Linoleic Acid	No	Possible Orally	Possible	Yes	Yes

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